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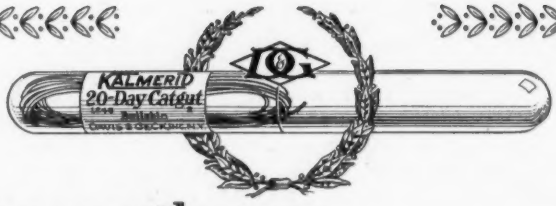

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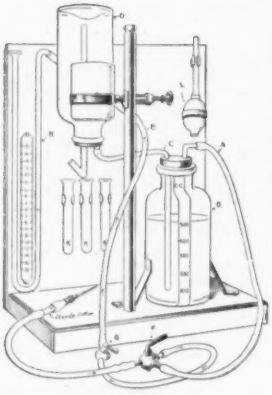

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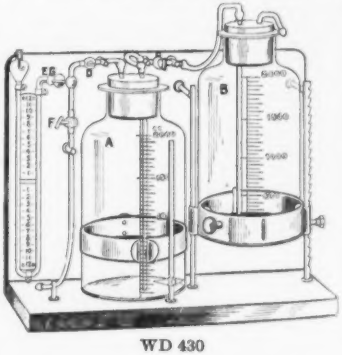

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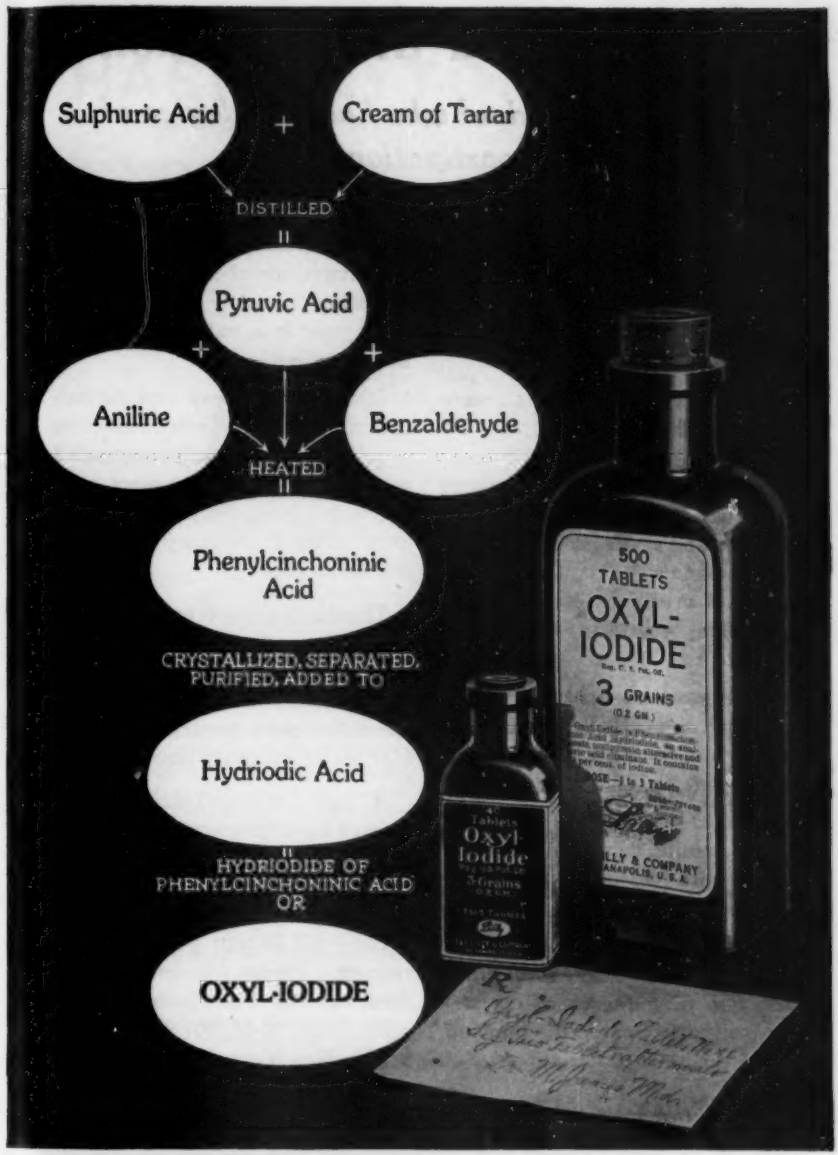

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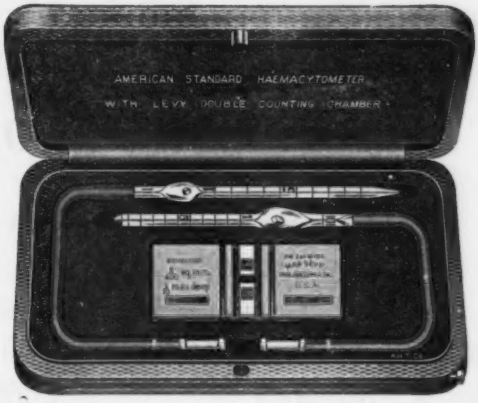

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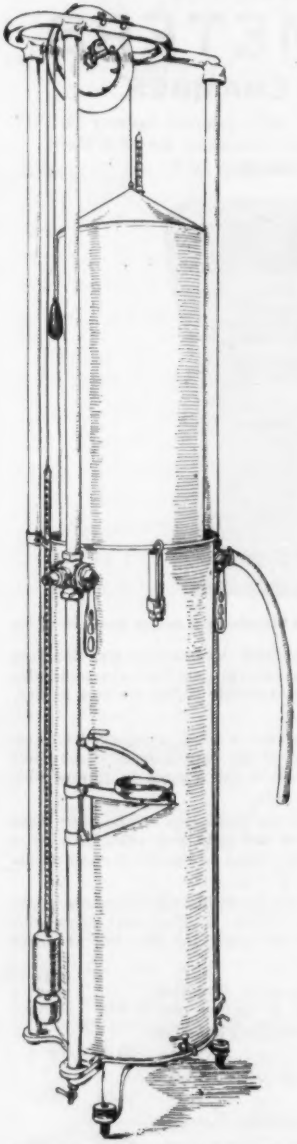

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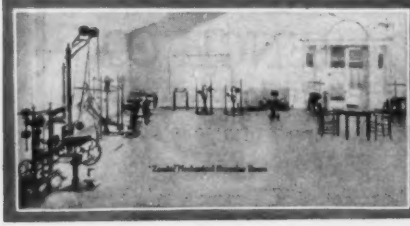

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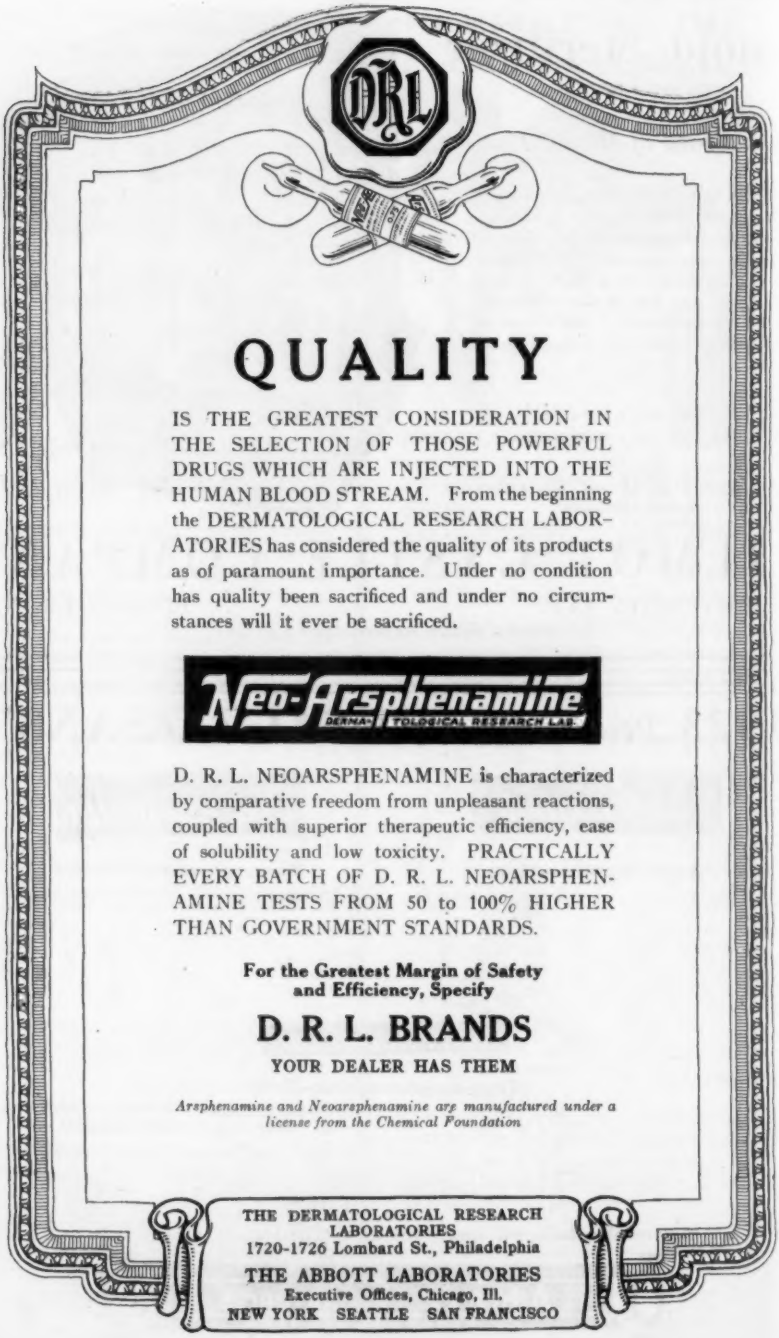

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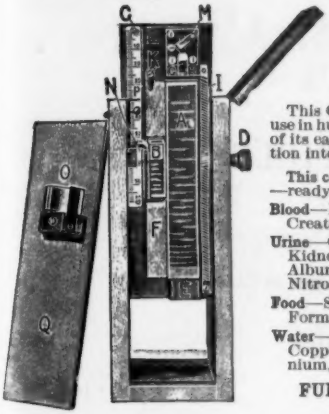

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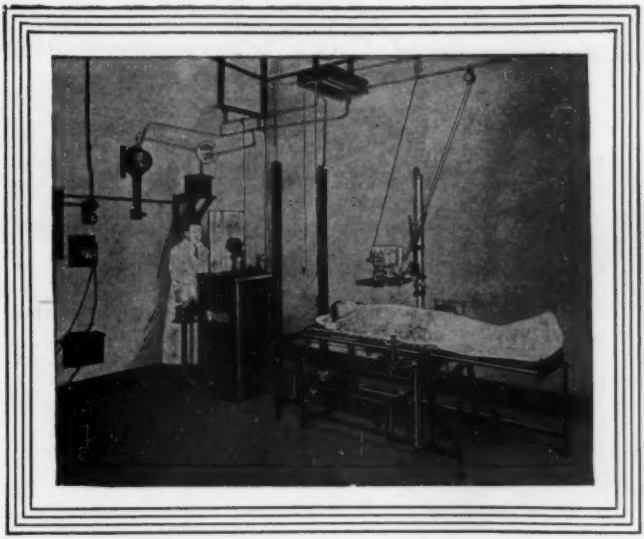

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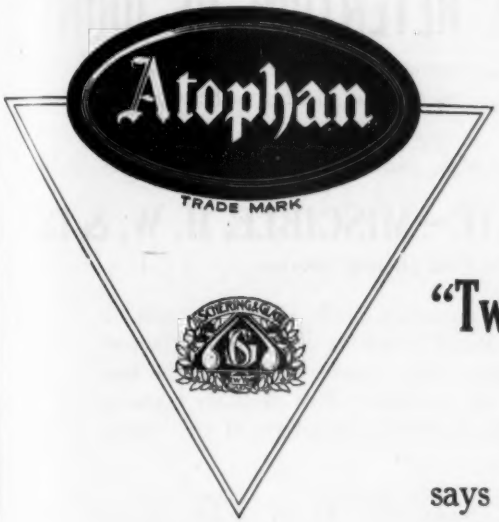

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FEBRUARY, 1923

ORIGINAL ARTICLES.

A CLINICAL INVESTIGATION OF TROPICAL SPRUE.[1]

By Bailey K. Ashford, M.D., Col. Med. Corps, U. S. A.

INSTITUTE OF TROPICAL MEDICINE AND HYGIENE, SAN JUAN, PORTO RICO.

The symptomatology of sprue is a complex. The principal factors in the production of this complex are, on the one hand, glandular insufficiency, and, on the other, colonization in the digestive tube of a superimposed specific organism, *Monilia psilosis*, the latter bringing out the typical clinical picture we know as sprue.

Instead of rehearsing a list of symptoms commonly observed, let us first analyze the results of a long, clinical study of the disease as it exists in Porto Rico, and then group the phenomena according to their source.

The usual sequence of events is about as follows:

1. Physiologic glandular deficiency due to one or more of the following conditions:

(*a*) Hereditary depression of cellular vitality.

(*b*) Long-continued exposure to a tropical climate.

(*c*) Lack of healthful exercise, lack of sufficient sleep, frequent pregnancies, long-continued lactation, irregular hours of eating and monotonous and ill-prepared or indigestible food.

(*d*) An ill-balanced diet in which inordinate quantities of vitamine-less cereal foods, sweets and lard or vegetable oil are preferred to fresh garden products, meat and butter fat.

(*e*) Previous wasting diseases, such as enterocolitis in childhood, dysentery, malaria, tuberculosis, syphilis and others of chronic course, especially those in which the appetite fails, or the nature of

[1] Published with permission of the Surgeon-General U. S. Army, who is not responsible for any opinion expressed or conclusions reached herein.

the disease suggests a long-continued restriction of normal alimentation.

2. The gradual development of the symptom-complex resulting from this condition in which are prominent:

(*a*) Asthenia.

(*b*) Acid dyspepsia.

(*c*) Excess of intestinal gas.

(*d*) Constipation with or without occasional attacks of indigestion and "loose bowels."

(*e*) Reduction in size of the liver.

(*f*) Loss of appetite and weight.

(*g*) "Nervousness" with palpitation of the heart, pains in the body, depression of spirits, sleeplessness and mental hebetude.

(*h*) Pallor.

(*i*) Disorders of menstruation.

(*j*) Pigmentation of skin, chiefly over the malar prominences and forehead.

3. The gradual or abrupt development of sore tongue or large white, frothy movements, or both, with a pronounced increase in all of the symptoms of glandular deficiency above recounted. In the characteristic picture of tropical sprue, *Monilia psilosis* can usually be demonstrated, in contrast with the preliminary condition in which this organism is usually absent, unless it has effected a foothold, but has not yet succeeded in completing the sprue syndrome. It is in these borderland cases between incomplete sprue and the syndrome of glandular insufficiency that clinical diagnosis is practically impossible without a positive laboratory finding. This difficulty is increased by a subjective sensation of slight burning in the tongue without visible lesions, common to both conditions. When, in addition to this, constipation alternates with loose bowel movements, the confusion is complete. Very little difficulty is experienced in diagnosing a fully developed classical case of sprue, but such a case will have reached a point in which pancreas, intestinal glands and liver are apt to be in a state of partial atrophy from which recovery is slow and laborious, no matter what treatment is employed.

While the above is the usual trend of events in the unfolding of the sprue picture, the exceptions to the rule are most striking and far from rare. Many times, perhaps in a third of my cases, there has been no reasonable doubt that food deficiency played no part whatsoever. Moreover, a goodly number of these showed no evidence of a previous glandular deficiency. A relatively small class of acute cases, recent arrivals from the North, in which, after a sharp attack of gastroenteritis, the full sprue syndrome appeared, is the culminating fact which demonstrates that sprue is not necessarily dependent upon either food deficiency or glandular insufficiency.

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On the other hand, about 12 per cent of our cases of sprue were negative, mycologically and serologically. Such were usually old chronic cases, often in a state of cachexia, or those in whom the tongue lesions and characteristic diarrhea, once prominent, were quiescent at the time of examination. The cachectic cases are to be considered practically as in a state of extreme glandular atrophy the result of sprue, and no surprise need be exhibited in finding no traces of the organism that produced the condition. The cases of undoubted sprue in a state of quiescence, while far more apt to give a positive blood reaction, are not much less apt to make a positive mycologic finding difficult if not well-nigh hopeless. While both of these classes are perfectly understandable from a scientific point of view, and for a like reason occur in syphilis and tuberculosis, they seem to furnish the scanty material from which men of excellent standing in the practice of medicine of the temperate zone draw the sweeping conclusion that *Monilia psilosis* has nothing to do with the production of sprue, even that there is no such disease as sprue at all. When we reflect that only 1.5 per cent, at most, of tropical people living in endemic zones have been found to harbor *Monilia psilosis* without showing its characteristic effects and contrast this with the fact that 87.6 per cent of our sprue patients are heavily infected with it, it does not seem necessary to enter into any further controversy with those who are probably not in a position to argue the point they themselves raise.

We are now prepared to consider the data which have been collected personally since 1908.

A few words are necessary before entering into these details in order to comprehend the scope of the work and the significance of certain necessary symbols.

Sprue was first announced to be a disease of Porto Rico by the writer in the summer of 1908. Hence the study from that time until the close of 1913 was purely clinical and epidemiological. In 1914, *Monilia psilosis* was identified as the direct cause of the disease, and from that date until 1917 studies were focussed on the mycologic study of tongue scrapings and feces in connection with only such a number of clinical cases as could be personally followed throughout their entire course. On return from France in 1920, where the writer engaged in the military operations of our land forces in the Great War, a series of clinical cases, checked upon by serologic study of the Laboratory of the Institute of Tropical Medicine and Hygiene of Porto Rico, was completed. In 1921, another series was undertaken and completed, checked upon by both mycologic and serologic examination by this Institute, and further contrasted with cases of pure glandular insufficiency, half of which were examined serologically and mycologically and found negative for *Monilia psilosis*.

Whereas the cases of the series 1908–1913 and 1914–1917 were

complete as far as outstanding signs and symptoms were concerned, particularly regarding the state of the tongue and feces, no fixed questionnaire had been adopted for all cases.

In 1920, however, a set of questions was prepared covering all of the usual phenomena clinically observed in sprue, and these same questions were propounded with fair regularity to all patients, whatever might be their affection, in the series of that year.

The questionnaire was amplified and rigidly observed in all cases for 1921, and by comparing the condition in sprue with that seen in glandular insufficiency and in other affections, a very clear picture of what we know as sprue is revealed.

The order of these questions was necessarily peculiar for practical purposes of history taking, but it will be conserved in this work.

The symbols used for brevity will also be adhered to for the same reason and the key to these tables is herein displayed.

Symbols Used in Classifying Pathologic Conditions in this Text.

D = *Digestive system.*

1 = Subjective burning in tongue without demonstrable evidence thereof. Ranges from slight irritation to sensation of burning.

1 = Burning in tongue with evident lesions on tip or tip and edges. Ranges from redness to excoriation.

1 = Raw tongue resembling a piece of raw beef.

2 = Acid gastric dyspepsia with fulness after eating, rawness and the belching up of a hot acrid fluid.

3 = Excessive intestinal gas.

4 = "Loose bowels," or "attacks of indigestion," alternating with constipation.

4 = Diarrhea, generally light in color, gaseous and lienteric, but the symbol also denotes bilious, mucous watery and particolored movements.

4 = Typical white, frothy stools of classical sprue.

5 = Constipation.

6 = Abdominal pain referable to intestine.

7 = Small liver.

7 = Unusually small liver.

8 = Nausea.

9 = Vomiting.

10 = Heat and burning in rectum.

11 = Heat and burning in vagina.

12 = Loss of appetite.

12 = Complete anorexia.

13 = Excess of saliva.

N = *Nervous system.*

1 = "Nervousness," ranging from nervous irritability to nervous excitability.

2 = Asthenia.

3 = Sleeplessness, fitful sleep, nightmare.

4 = Pains in trunk and limbs, ranging from a feeling of muscular soreness on overexertion to definite neuralgia and neuritis, general or localized.

5 = Palpitation of the heart, cardiac irregularity.

6 = Psychic depression.

7 = Tingling, burning and coldness of hands and feet, a tendency for upper and lower extremities to go to sleep.

8 = Forgetfulness. Mental hebetude.

P = *Unclassified.*

1 = Sallowness to pallor.

1 = Extreme pallor.

2 = Vertigo.

3 = Dysmenorrhea.

4 = Amenorrhea.

5 = Headache.

6 = Subcutaneous extravasation of blood without apparent cause or on slight contusion.

7 = Brown pigmentation resembling nut stains on skin. Usually symmetrical and most common and prominent over malar prominences, cheeks and forehead.

8 = Excessive menstrual flow, to menorrhagia.

9 = Irregular menstruation.

10 = Scanty menstrual flow.

G 2 = Loss in weight.

This bizarre grouping of signs and symptoms, including all of the usual phenomena accompanying sprue, may seem unsystematic and inexact. It should be remembered, however, that it is necessary to consider the psychologic attitude of the sick man in making up a questionnaire, in order to allow the patient himself, with least amount of what he would consider obstruction, to expand the picture he would like to draw. The sense of good order and exactness of the physician may appear to suffer thereby, but in the long run much more information is obtained.

Therefore, once adopted, this order of questioning has been followed throughout the series of 1920–21. Although it can now, and will be later, simplified and increased in scope, it did not seem justifiable to make these changes until the series under analysis were completed.

Indefiniteness is not a rare quality in the average patient when relating what he feels that is abnormal, no matter what the disease or condition may be; but the average patient suffering from sprue, beyond his tongue and bowel symptoms, is notoriously indefinite in rehearsing his wretchedness. He hardly knows how to express himself, hardly realizes what it is that makes him a sick man, beyond his unruly "stomach," his loose bowels and his sore tongue. It is all very well to say that in history-taking one should not ask leading questions, but with most sprue patients I have seen, one would

never find out what they had if clear questioning is not employed. It should be borne in mind that mental confusion and forgetfulness in sprue is a feature of the disease, so that it is well to begin by saying, "Now tell me all that you can about what ails you." Then proceed to ask question after question, in the order given, carefully pinning the man or woman down to as exact and uncolored statement of fact as may be possible. This being concluded, a physical examination on the table is to be made, and finally all clinical laboratory analyses bearing on the individual case, including mycologic and serologic examinations for moniliasis.

Exclusive of laboratory work, the primary examination of each case requires for its thorough accomplishment not less than half an hour and often much more.

It seems hardly necessary to say that answers to questions in the taking of the history should embrace the entire period from which the patient has suffered from his affection and are not to be confined to symptoms on the day of his first visit. This is needful to avoid a negative of characteristic phenomena which generally occur only from time to time and which may constitute an important part of the evidence upon which the clinical diagnosis of sprue may be justified.

Series of 1908–1913. This period corresponds to the clinical and epidemiological study, begun in 1908, which culminated in the identification of *Monilia psilosis*. These cases, therefore, possess no laboratory guide or check and only very clear pictures of classical sprue were so regarded. Among the doubtful cases many more must have been included, but, as the writer was depending chiefly upon Manson's work on *Tropical Diseases*, no departure from the criterion therein expressed of what should constitute an unquestioned clinical entity was permitted. The cardinal symptoms, sore tongue, gastric disorder, excess of intestinal gas and diarrhea, were faithfully recorded in all, but the importance of the remainder of the signs and symptoms, found in the questionnaire above detailed, were not appreciated and were only noted when the patient happened to mention them in his personal narrative. Therefore, for statistical purposes, all save these cardinal symptoms must be discarded.

Series of 1914–1917. (Mycologic Series.) This series began with the discovery of a pathogenic yeast-like budding fungus, later designated by myself *Monilia psilosis*, in the scrapings from the inflamed tongue of a young Porto Rican boy. Within a short time, in three more cases, the same organism was recovered, one from a child of two or three years whose only symptom was a raw tongue, one from a young woman with a life history of gastrointestinal derangement and an incipient tuberculosis, and one from a continental American in the last stages of uncomplicated acute sprue, from which he later died. These four cases were studied mycologi-

cally for some months with uniform mycologic findings; later some twenty more cases were added and the tedious mycologic study repeated; finally, the series was continued to include a total of 476 assorted cases of which 246 were clinically sprue.

A mycologic study of tongue scrapings and feces was made in 448 of the 476 cases; in 225 cases of clinical sprue, of which 75 per cent were positive for *Monilia psilosis*, and in 223 cases not clinically sprue, of which 1.3 per cent were positive for this organism.

TABLE 1.—CONSOLIDATED TABLE SHOWING RELATIVE FREQUENCY OF CARDINAL SYMPTOMS OF SPRUE IN ALL FOUR SERIES (1572 CASES)

	All our series.[1]	Percentage.
D 1	494	31
1	303	19
1	319	20
All 1	1116	71
2	1259	80
3	1329	84
4	531	34
4	258	17
4	426	27
All 4	1215	77

TABLE 2.—RELATIVE PROPORTION OF CASES OF COMPLETE AND INCOMPLETE SPRUE IN A TOTAL OF 1309 CASES.

	Series 1914–17.	Series 1920.	Series 1921.	Total.	Per cent.
Both D 1 and D 4	158	285	370	813	62
One or the other	24	140	171	335	26
Neither D 1 nor D 4	8	78	75	161	12
Total	190	503	616	1309	100

Explanation of Graphs. The panels in each fan are rounded off at their broad extremity and bear a number corresponding to symbols already explained in this text. The lines within each panel stand for the percentage of cases which the clinical phenomenon or phenomena, represented by the symbol, bear to the total cases in this series. Each line within the panel represents 5 per cent or major fraction thereof. No lines appear where less than 7 per cent of the cases showed the phenomenon.

[1] The separation of cases suffering from sore tongue into three degrees (D 1, *1* and **1**) and of those with diarrhea into D 4, *4* and **4**, was not consistently carried out in the 1920 series, but as the total number of cases of sore tongue and diarrhea yielded a percentage to total cases of sprue almost identical with corresponding totals in 1921, the relative number in each one of the three groups under D 1 and D 4, 1920, has been calculated from the percentage in 1921.

The important point in interpreting these fans is to remember that 453 of the 616 cases of sprue and 124 of the 259 cases of glandular insufficiency were examined in the laboratory, the first being all

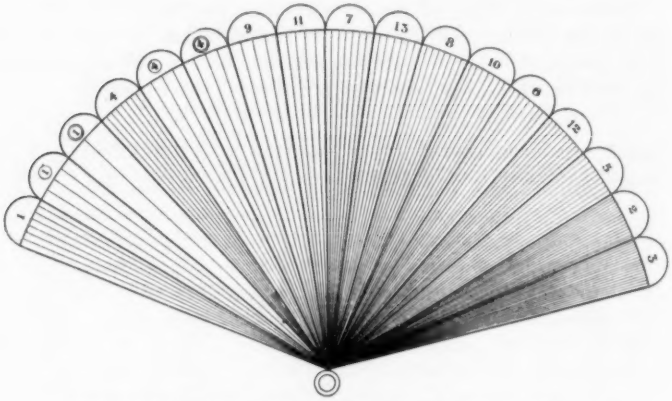

FIG. 1.—Series 1921; 616 cases. Digestive symptoms. Sprue.

positive for *Monilia psilosis*, the second all negative. The examinations in laboratory were only made *once* in 98 per cent of these cases. Had time and personnel as well as constancy on the part of

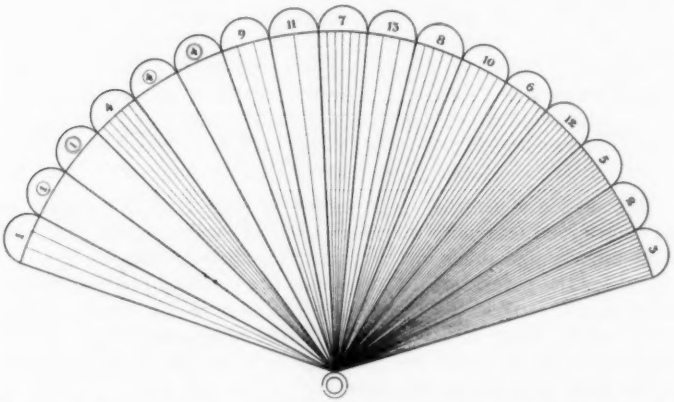

FIG. 2.—Series 1921; 259 cases. Digestive symptoms, glandular insufficiency in Porto Rico.

the patients permitted, a much higher percentage of positive results in the sprue series might have been obtained. As to the series of cases of glandular insufficiency, mycologic study of the feces daily

for a continued period would have undoubtedly revealed a stray colony now and then, as *Monilia psilosis* is a widespread fungus in Porto Rico and frequently must pass through the intestinal canal as

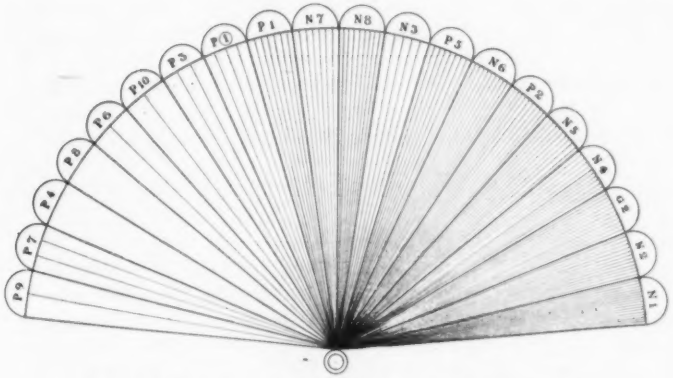

FIG. 3.—Series 1921; 616 cases. Assorted symptoms. Sprue.

a *voyageur*, or, as Anderson so well expresses it, "like so much waste food," but without colonizing. When it colonizes in the intestinal tract then we may expect its pathogenic effect. The best way to bring out the presence of an infection by *Monilia psilosis* is to sow

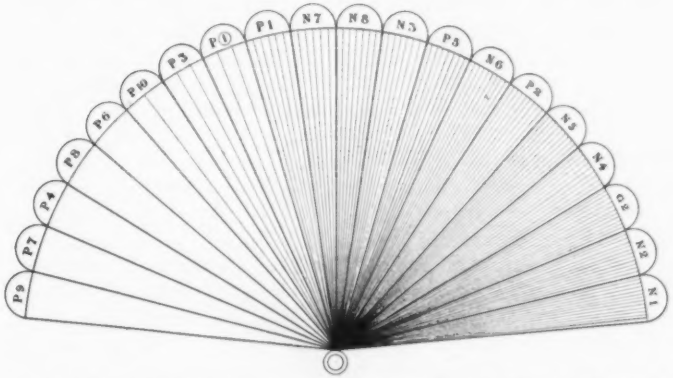

FIG. 4.—Series 1921; 259 cases. Assorted symptoms, glandular insufficiency in Porto Rico.

in Sabouraud agar Petri plates by Anderson's method, *i. e.*, by making a hundred separate points of contact with a platinum loop soiled in the feces and taking a percentage of positive colonies.

This series was intended to be purely a clinical versus mycologic study, but in 1916–1917 the feasibility of applying the complement-deviation test for diagnosis became evident and 88 of the 225 cases

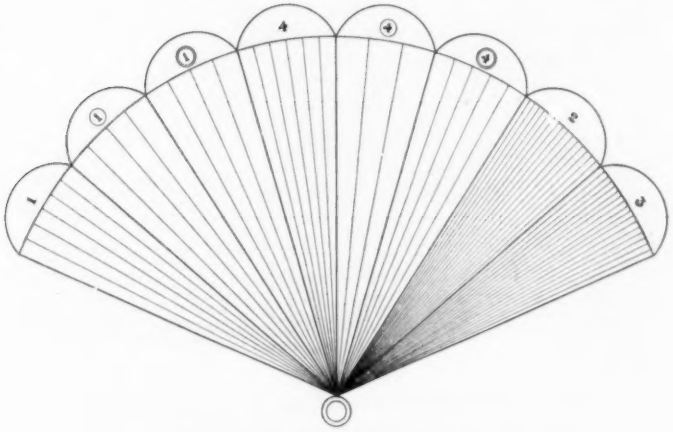

FIG. 5.—All series; 1572 cases. Sprue.

of sprue were thus examined. In this way 20 cases which had been mycologically negative were shown to be serologically positive,

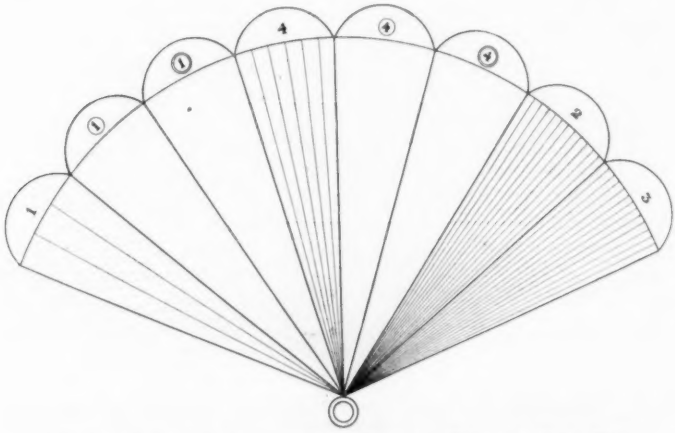

FIG. 6.—Series 1921; 259 cases. Glandular insufficiency in Porto Rico.

raising the percentage of positive laboratory findings to 84 per cent. Had all of the 225 been available for this blood test this rate would have probably been above 90 per cent.

The tabulation of clinical phenomena is as in the preceding series. No questionnaire was adhered to, save as concerns the tongue symptoms, acid gastric dyspepsia, excessive intestinal gas and diarrhea (D 1, *1*, **1**, 2, 3, 4, *4*, **4**).

In this series the individual grouping of the four cardinal symptoms of sprue was consolidated in 211 cases, 84 per cent of which were confirmed by laboratory finding.

Cases with typical raw tongue and frothy, white diarrhea, 92, or 48 per cent.

Cases with typical raw tongue, with or without diarrhea, 101, or 53 per cent.

Cases with tongue raw at tip and edges, with or without diarrhea, 22, or 11 per cent.

Cases in whom only a sensation of burning was felt, with or without diarrhea, 44, or 22 per cent.

Cases with both sore tongue and diarrhea, 158, or 83 per cent.

Cases with one or the other of above symptoms, 24, or 13 per cent.

Cases with neither one nor the other, 8, or 4 per cent. Total, 190.

In the spring of 1917 these studies were abruptly suspended by the Great War, which scattered the group of men who formed the Institute of Tropical Medicine throughout the armies of the United States, and for a period of three years the writer was unable to take up the tangled skein of tropical sprue. But such was the spirit of the Institute that the other members kept the work alive. Adding valuable confirmatory data to the investigation begun in 1908, Drs. Gutierrez Igaravidez, Dr. González Martinez and Dr. Carl Michel, each separately, the first while in the training camp of the 2d Brigade of the 81st Division, the second in his personal work and at the close of the war in Paris and Barcelona, and Dr. Michel in the laboratory and later in the United States, kept up a persistent and brilliant campaign to extend the application of what was up to that time known.

In 1920 the writer returned to Porto Rico, thanks to the scientific spirit of his military chief, to complete this series of studies, and since that time, with the same technicians who had for ten years diligently kept up the laboratory work, this investigation has been going forward. It is difficult to estimate the value of the work of these technicians, Messrs. José Loubriel and Figueroa, who throughout a period of these three years had become as expert as ourselves in the routine laboratory methods of revealing the presence of *Monilia psilosis*, mycologically and serologically. Up to 1917, the writer had personally accomplished every step in this mycological laboratory work in each case, even to the preparation of media, the technicians then in training duplicating this work under my supervision in order to familiarize them thoroughly with every possible laboratory situation. Dr. Michel and Dr. González trained them in the special serology of moniliasis. The object, on my part, was

to continue these investigations by permitting our technicians to render the laboratory reports in cases of which they knew nothing clinically and free me for the clinical study and treatment of a larger series of cases in order to submit each case of sprue to the severe test of a laboratory analysis to determine the presence or absence of *Monilia psilosis* in which I, the interested party, would be eliminated. In the meantime I continued research laboratory work in *Monilia psilosis* and its congeners and with Drs. Gutierrez and González, supervised the clinical laboratory work.

Series of 1920. This was principally a clinical versus serologic study, mycological investigations being employed only from time to time for corroboration, or in certain cases, but not systematically, in which a typical case of sprue had been reported as negative serologically.

In all, 503 cases of sprue, out of a total of 1267 patients examined, were found. In contemplation of these figures it must be remembered that I was dedicating practically my entire attention to sprue, and the majority of those who came for examination were either sent to me from all over the Island by other physicians as cases suspicious of, or positive for, that disease, or were persons who had themselves come to believe that they were suffering from sprue, whose complete clinical picture had by this time become almost universally recognized by laymen throughout the Island.

Series of 1921. The development in medical science of the recognition of a syndrome of glandular insufficiency came to put the finishing touches upon this study of sprue in Porto Rico, and we believe, all of us of the Institute, and an ever-increasing number of observing practitioners in these tropics, that it may be accepted with a fair degree of certainty that the veil of mystery which has enshrouded tropical sprue has at last been rent in twain.

It is curious how the forces of our little group in the Institute of Tropical Medicine have complemented one the other. At the very outset of the modern work on sprue, back in 1914, Dr. Gutierrez Igaravidez stoutly maintained that the underlying cause of sprue was a glandular disturbance. Dr. W. W. King, who was one of the founders with us of the Porto Rico Anemia Commission for the study of uncinariasis and later of the Institute, believed that whatever sprue might be, *Monilia psilosis* seemed to have something to do with its manifestations. Dr. González Martinez, without commenting upon the conception of an intestinal moniliasis, silently worked out the specific serological reaction and became gradually more and more convinced of the importance of this fungus in its etiology, finally taking a stand publicly in defense of this conception. All have persistently and dispassionately sought the light while always remaining loyal to the Institute.

While I am only reporting my own personal work, I do not wish to leave the idea that no other work on sprue has been accom-

plished here. The others, members of the Institute, have their case records and will some day, it is to be hoped, express their own experiences and opinions regarding this disease.

In this series of 1921 the study made was for the purpose of comparing clinical, mycological and serological data, as well as for separating out the cases of glandular insufficiency.

TABLE 3.

	Clin. sprue confirmed by laboratory, 385 cases.		Clin. sprue not examined in laboratory, 163 cases.		Clin. sprue negative in laboratory, 68 cases.		Total sprue, 616 cases.		Clin. not sprue and negative in laboratory, 238 cases.		Cases of glandular insufficiency, 259 cases.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
D 1 . .	128	33	70	43	29	43	227	37	38	16	44	17
1 . .	57	15	41	25	24	35	122	20	6	3	6	2
1 . .	39	10	24	15	9	13	72	11	1	½		
All 1 . .	224	58	135	83	62	91	421	68	45	18½	50	19
2 . .	326	84	145	88	64	94	535	86	108	45	162	62
3 . .	337	87	147	90	65	95	549	89	138	58	169	65
4 . .	154	40	65	40	25	37	244	39	62	26	76	29
4 . .	67	17	35	21	21	30	123	20	21	9	19	7
4 . .	62	16	38	23	20	29	120	19	7	3		
All 4 . .	283	73	138	85	66	96	487	79	90	38	95	37
5 . .	176	45	78	48	42	62	296	48	97	40	140	54
6 . .	135	35	78	48	78	70	261	42	31	34	92	35
7 . .	94	24	55	34	27	40	176	28	52	22	61	24
7 . .	23	6	15	9	10	15	48	8	11	5	11	4
8 . .	153	39	64	39	37	54	254	41	59	25	69	26
9 . .	76	19	39	24	25	37	140	23	33	14	40	15
10 . .	141	36	68	42	44	65	253	41	53	22	62	24
11 . .	47	20	32	20	19	28	87	14	17	7	19	7
12 . .	153	39	72	44	46	68	271	44	74	31	96	37
12 . .	26	6	9	5	4	6	39	6	6	2	19	7
13 . .	121	31	50	31	33	48	204	33	37	16	43	16
N 1 . .	255	66	106	65	60	88	521	84	121	50	168	65
2 . .	235	60	103	63	54	80	392	63	109	45	156	60
3 . .	171	45	81	50	47	69	164	26	75	31	94	36
4 . .	208	54	86	53	50	73	344	55	92	39	133	51
5 . .	184	47	80	49	46	68	310	50	86	36	127	49
6 . .	191	50	72	44	53	78	316	51	82	34	113	43
7 . .	125	32	59	36	48	70	233	37	56	24	75	29
8 . .	158	40	71	44	46	68	275	44	67	28	89	34
P 1 . .	127	33	57	35	28	41	212	34	56	24	78	30
1 . .	82	21	39	24	16	23	137	22	36	15	42	16
All 1 . .	209	54	96	59	44	65	349	56	92	39	120	46
2 . .	189	48	76	46	45	66	310	50	95	39	120	46
3 . .	39	10	10	6	7	10	56	9	13	5	22	8
4 . .	17	4	2	1	6	9	25	4	7	3	10	4
5 . .	145	37	70	43	37	54	252	41	77	32	109	42
6 . .	36	9	16	10	11	16	63	10	11	5	17	7
7 . .	47	12	14	9	17	25	78	13	12	5	14	5
8 . .	19	5	5	3	3	4	27	4	10	4	10	4
9 . .	16	4	5	3	9	13	30	5	7	3	9	3
10 . .	21	5	11	7	1	1	33	5	14	6	16	6
G 2 . .	214	55	92	56	50	73	356	57	186	78	104	40

The questionnaire was here placed rigidly in force and its data are considered as reliable as ordinary human observation can make them. In this table, separate classification of the phenomena observed in 259 cases of glandular insufficiency has been made. Table of clinical phenomena observed in 616 cases of sprue, in 238 cases which were clinically not sprue and negative by laboratory methods, and in 259 cases of glandular deficiency, giving the number of cases suffering from the condition denoted by each symbol and the percentage this number bears to the total number in each group. Of the cases listed as cases of glandular insufficiency, 124 were examined by laboratory methods and were negative. These 124 cases are also included under "cases clinically not sprue and negative in laboratory" in column 5. The remaining 135 were clinically cases of glandular insufficiency but were not examined by laboratory methods although entirely similar to the 124 which were so examined.

In table 3 it will be noted that the clinical picture in the cases which were negative in the laboratory was more vivid than in those which were positive. This obtains in every series and results from a combination of two factors: (1) The cases of complete sprue confirmed by the laboratory were augmented by a number of incomplete cases which lowered the intensity of the composite picture; (2) severe and cachectic cases are often negative when chronic and quiescent, *i. e.*, when, at the time of examination, they are bereft of active inflammatory changes in the mucosæ. In fact, very cachectic or very chronic cases, or those in which active symptoms of sprue are temporarily in abeyance, are frequently negative, mycologically or serologically, or both, as occurs in syphilis and tuberculosis, and for the same reasons. The increased number of sore tongues and diarrheas in these cases does not necessarily refer to the condition at the time of examination, but to the past history as well.

The severe type in purely clinical cases without laboratory examination in this table is due to the fact that such cases were so clearly sprue that no serologic examination could be urged for diagnostic purposes in certain persons who strongly objected thereto, or in those whose physical condition made the effort palpably unjustifiable, from the standpoint of the patient.

The most interesting feature of this table is the comparison which can be made between identical symptoms in sprue, on the one hand, and glandular deficiency on the other. In making this comparison it should be remembered that:

1. Of the 616 cases of sprue, 453 were examined by laboratory methods and 85 per cent yielded a positive finding for *Monilia psilosis*.

2. Of the 259 cases of glandular deficiency, 124 were examined by laboratory methods and all were negative for *Monilia psilosis* the rest were not examined in the laboratory.

All of the phenomena in the syndrome of glandular insufficiency were more frequent and, clinically, far more vivid in sprue, generally about double that of the former condition. But the salient point is found in that in sprue the tongue lesions are over fifteen times, and the frank diarrhea over five times, as frequent as in glandular insufficiency. In fact, the strictly classical raw tongue and white, frothy diarrhea were never found in glandular insufficiency. The graphic exposition of the clinical difference between these two conditions can be better appreciated by reference to the fans prepared to illustrate the point.

TABLE 4.—LOSS OF WEIGHT IN SPRUE AND GLANDULAR INSUFFICIENCY.

Loss in weight.	Clin. sprue confirmed by laboratory, No. of cases.	Clin. sprue not examined in laboratory, No. of cases.	Clin. sprue negative in laboratory, No. of cases.	Total sprue, No. of cases.	Glandular insufficiency, No. of cases.
Under 10 lbs. . .	3	2	1	6	7
10 to 15 " . .	19	4	1	24	5
16 to 20 " . .	11	5	1	17	2
21 to 30 " . .	18	4	4	26	2
31 to 40 " . .	11	1	2	14	
41 to 50 " . .	4	2	4	10	1
51 to 60 " . .	1	1	..	2	
Number weighed .	67	19	13	99	17
Average loss . .	24 lbs.	25 lbs.	31 lbs.	...	15 lbs.

TABLE 5.—GENERAL RÉSUMÉ OF ALL FROM SERIES CONTAINING 1595 CASES OF SPRUE.

	Series 1908–13.	Series 1914–17.	Series 1920.	Series 1921.	Total.	Per cent.
Cases of sprue without laboratory examination .	230	21	88	163	502	32
Sprue confirmed by laboratory methods . . .	...	189	379	385	953	60
Same negative by laboratory methods . . .	....	36	36	68	140	8
Total sprue . . .	230	246	503	616	1595	100
Cases suspicious of sprue but not examined in laboratory[1]	328	...	...	...	328	
Cases definitely not sprue, negative by laboratory examination	...	226	180	238	645	
Carriers	...	1	6	3	10	
Cases definitely not sprue not examined in laboratory; not classified . .	3159	3	578	782	4519	
Total	3717	476	1267	1639	7097	

[1] All of the "cases suspicious of sprue" were so diagnosed clinically, as these studies were made previous to the discovery of the causal organism.

TABLE 6.—TABLE OF CLINICAL PHENOMENA OBSERVED IN 942 CASES OF SPRUE CONFIRMED BY LABORATORY METHODS GIVING THE NUMBER OF CASES SUFFERING FROM THE CONDITION DENOTED BY EACH SYMBOL AND THE PERCENTAGE THIS NUMBER BEARS TO THE TOTAL NUMBER IN EACH GROUP.

	1914–17, 178 cases.		1920, 379 cases.		1921, 385 cases.		Total.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
D 1	39	22	..	..	128	33		
1	20	11	..	..	57	15		
1	99	56	..	..	39	10		
All 1	158	89	231	60	224	58	603	65
2	146	82	300	78	326	84	772	82
3	160	90	319	83	337	86	816	87
4	39	22	..	..	154	40		
4	6	3	..	..	67	17		
4	114	64	..	..	62	16		
All 4	159	89	246	64	283	73	688	73
7	66	37	80	28	117	30	263	28
P 1	90	50	178	46	209	54	477	50

TABLE 7.—TABLE OF CLINICAL PHENOMENA OBSERVED IN 149 CASES OF SPRUE, NEGATIVE ON LABORATORY EXAMINATION, GIVING THE NUMBER OF CASES SUFFERING FROM THE CONDITION DENOTED BY EACH SYMBOL AND THE PERCENTAGE THIS NUMBER BEARS TO THE TOTAL NUMBER IN EACH GROUP.

	1914–17, 45 cases.		1920, 36 cases.		1921, 68 cases.		Total.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
D 1	9	20	..	..	29	43		
1	5	11	..	..	24	35		
1	23	51	..	..	9	13		
1	37	82	35	97	62	91	134	90
2	32	71	28	77	64	94	124	83
3	36	80	34	94	65	95	135	90
4	8	18	..	..	25	37		
4	1	2	..	..	21	30		
4	32	71	..	..	20	29		
All 4	41	91	34	94	66	96	141	95
7	9	20	10	27	27	40	46	30
P 1	11	24	12	37	44	64	67	45

TABLE 8.—TABLE OF CLINICAL PHENOMENA OBSERVED IN 481 CASES OF SPRUE, NOT EXAMINED IN LABORATORY, GIVING THE NUMBER OF CASES SUFFERING FROM THE CONDITION DENOTED BY EACH SYMBOL AND THE PERCENTAGE THIS NUMBER BEARS TO THE TOTAL NUMBER IN EACH GROUP.

	1908–13, 230 cases.		1920, 88 cases.		1921, 163 cases.		Total.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
D 1	34	15	..	..	70	43		
1	56	24	..	..	41	25		
1	166	28	..	..	24	15		
All 1	156	67	78	88	135	83	369	77
2	152	65	65	75	145	88	362	75
3	153	66	78	88	147	90	378	78
4	64	27	..	..	65	40		
4	39	17	..	..	35	21		
4	74	32	..	..	38	23		
All 4	177	78	71	80	138	84	386	80
7	..	...	..	..	70	43		
P 1	..	..	..	..	96	60		

TABLE 9.—GRADE OF SPRUE IN 1470 CASES.

Grade.	Series 1908–13.	Series 1914–17.	Series 1920.	Series 1921.	Total.	Per cent.
Light	9	32	81	80	202	14
Moderate	38	72	265	269	644	44
Severe	38	90	157	237	522	35
Cachectic	20	52	..	30	102	7
Total	105	246	503	616	1470	100

TABLE 10.—CARRIERS.

		1	6	3	10	

Percentage of carriers to 645 cases definitely not sprue and examined in laboratory = 1.5.

Percentage of carriers to 1093 cases of sprue, 0.9.

NOTE.—In constructing the graphs the percentages for D 11 and P 3, 4, 8, 9 and 10 are calculated from the number of women in the series. This makes an apparent discrepancy with the table of total percentages.

THE TOTAL CIRCULATING VOLUME OF BLOOD AND PLASMA IN CASES OF CHRONIC ANEMIA AND LEUKEMIA.[1]

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Since the introduction of methods for the determination of blood volume applicable to clinical study, numerous estimations have been made in cases of chronic anemia. The volumes obtained in a given type of anemia, for example in pernicious anemia, have varied markedly even when the same investigator employed a single method. Corroboration or disproof of such results is important because of the well-recognized fact that in health the blood volume is remarkably constant. Therefore, shortly after Keith, Rowntree and Geraghty introduced the dye method for estimating blood and plasma volume, they made determinations in a few cases of chronic anemia. The early results indicated that both plasma and blood volumes might be little altered. Later, in a study of one case of pernicious anemia, the plasma volume was found to be definitely greater than in the normal controls, although the total blood volume was not increased. Subsequent estimations by the writer in a series of 14 cases of chronic anemia confirmed the original findings. Several cases showed but little deviation from the normal, while others showed a distinctly high plasma volume. Repeated determinations in these latter cases gave constantly high plasma values, although the total blood volume was not uniformly increased. Similar variations in total plasma were observed in 10 cases of chronic leukemia with this difference, that in cases of leukemia with high plasma contents the total blood volume was more often increased. Repeated determinations made periodically in individual cases in this series revealed distinct volume changes. The object of the present communication is to emphasize the fact that in chronic anemia and leukemia variations occurring in blood and plasma volume should be considered in evaluating the blood picture and other clinical findings.

Methods. The blood and plasma volumes were determined by the dye method introduced by Keith, Rowntree and Geraghty.[2]

[1] Read before the American Society for Clinical Investigation, Washington, D. C., May, 1922.

[2] *Relation of Blood Volume to Body Weight and Body Surface.* Dreyer and Ray believe that the blood volume in mammals is proportional to body surface and not to body weight. Accordingly they consider that the practice of expressing the blood volume in percentage of body weight is misleading, particularly when comparing individuals in any given species that differ greatly in weight. In order to ascertain by the dye method whether in normal adults the relation between blood volume and body surface was more constant than that between blood volume and body weight, data were obtained from ten persons in our previous series of normal male controls.

Comparison of this indirect method with other procedures has been made repeatedly by Whipple, Harris, and others. Whipple concludes from his experiments that the dye method gives remarkably constant results for total plasma, but considers that the value obtained for total circulating blood is higher than the amount actually present. That the absolute values for whole blood obtained by the dye method may be slightly higher than the actual amount of blood present seems probable on theoretical grounds. As yet there is no one method, not even any of the many modifications of the original Welcher direct method, that is free from obvious error. However, relative changes in blood volume can be definitely determined by the dye method. The hemoglobin estimations were made on venous blood by Palmer's modification of the Haldane method. Contrary to some workers, I have found that the 20 per cent standard hemoglobin solution will keep satisfactorily for several months provided the proper precautions are followed. Centrifuge tubes graduated to 10 cc containing 0.01 gm. of dry sodium oxalate were used for the hematocrit reading. The hematocrit tubes were then centrifugalized for twenty minutes at a speed of three thousand revolutions each minute. It should be noted that after centrifugalizing leukemic blood the line of demarcation between the red and white cell layers may be distinct or it may be scarcely perceptible. The erythrocyte and leukocyte counts were made in the usual manner, Hayem's solution and 1 per cent acetic acid being used as diluents. The basal metabolic rate[3] was determined in the leukemic patients by the gasometer method of Tissot.

The surface area was estimated according to the height and weight formula of Du Bois. The greatest variation in weight was 56.1 and 90.4 kg. and in height 162.5 and 183.1 cm. The average number of cubic centimeters of blood for each kilogram was 84.7 and the number of liters of blood for each square meter averaged 3.16. In considering the extreme variations from these average figures, the percentage deviations were slightly less marked when computed according to surface area than to body weight. But if the percentage deviation of each individual determination from the general mean were averaged, the values derived from surface area were more constant. Similar results were obtained when the plasma volume in 29 normal males was compared to body weight and body surface. The average values for plasma volume in these normal persons were 48 cc for each kilogram and 1.78 liters for each square meter. Although these results, limited to normal adults, showed no marked difference, whether the blood and plasma volume were computed as a function of the body weight or surface area, still the deviation from the average was distinctly less when the surface area was considered. These findings seem to indicate that the blood volume is a function of the body surface rather than of body weight. Further study of this question is desirable before a positive conclusion can be made. I am at present carrying out an investigation which includes normal persons exhibiting greater variations in age, weight and height, and also different species of animals. The blood and plasma volumes are expressed in relation to body weight, except in the cases of leukemia; in these the results are expressed both in relation to body weight and body surface.

[3] Boothby and Sandiford. (I am indebted to Dr. W. R. Campbell, University of Toronto, for the basal metabolic-rate determinations made in Toronto.)

TABLE 1.—PERNICIOUS ANEMIA.

Case.	Date.	Age and sex.	Weight, kg.	Hemoglobin, per cent.	Hematocrit, erythrocytes, per cent.	Erythrocytes.	Leukocytes.	Plasma, cc.	Plasma, cc. for each kg.	Blood, cc.	Blood, cc. for each kg.
26827 H. W. B.	July 12, 1919	63	..	35	..	1,200,000	13,000				
	Oct. 9, 1919	M.	52	16	6	...	...	4069	78	4330	83
	Oct. 18, 1919	..	51	26	12	...	...	4068	78	4610	88
	Nov. 21, 1919	..	46	23	..	704,000	3,400				
	Dec. 7, 1919	..	..	..	..	672,000	2,200				
26824 W. R.	Aug. 10, 1919	56	..	..	..	1,800,000					
	Sept. 27, 1919	M.	..	25	..	1,200,000	1,500				
	Nov. 14, 1919	..	46	23	8	1,050,000	1,300	3580	78	3900	85
	Dec. 12, 1919	..	..	21	..	974,000					
	Dec. 30, 1919	..	47	33	15	1,062,000	2,200	3460	73	4070	87
	Jan. 12, 1920	..	47	29	..	1,000,000	2,200				
	Mar. 1, 1920	..	..	60							
	Mar. 17, 1920	..	47	84	34	2,800,000	4,900	3300	70	5000	106
	April 5, 1920	..	47	84	..	3,200,000	3,200	...	..	...	
	April 16, 1920	..	51	88	32	...	...	3200	62	4705	92
26823 C. M.	Dec. 31, 1919	55	51	32	..	1,470,000	7,600				
	Jan. 5, 1920	M.	51	46	21	1,990 000	...	3395	66	4295	84
26826 C. H.	Mar. 13, 1920	44	65	62	24	2,700,000	3,600	3950	60	5300	81
	April 7, 1920	M.	63	80	33	...	2,800	3480	55	5195	82
27601 R. G.	April 12, 1920	41	52	47	17	1,500,000	4,400	3135	60	3825	73
	April 27, 1920	M.	..	34	..	1,300,000					
	May 17, 1920	..	..	22	..	1,130,000	5,600				
	June 7, 1920	..	47	26	10	900,000	...	3265	69	3630	77
	July 14, 1920	..	..	28	..	870,000	5,200				
	Aug. 19, 1920	..	..	90	..	2,472,000	3,000				
27602 E. H.	May 22, 1920	52	46	50	..	1,600,000					
	June 1, 1920	F.	46	35	13	1,000,000	5,000	2555	55	2935	64
	June 26, 1920	..	..	25	..	770,000	4,000				
	July 5, 1920	..	..	19	..	600,000					
28618 S. B.	June 12, 1920	57	46	16	..	650,000	6,800				
	June 26, 1920	F.	45	41	20	2,150,000	...	3660	81	4575	102
	July 22, 1920	..	49	80	..	3,300,000					
	Aug. 27, 1920	..	..	71	..	3,170,000	5,400				
	Oct. 27, 1920	..	..	22	..	1,000,000	6,000				
A258285 G. A. McK.	April 27, 1921	53 M.	62	69	27	2,100,000	7,400	3680	59	5040	81
A355666 W. S.	May 4, 1921	39 M.	70	46	20	2,040,000	4,200	3655	52	4570	65
A357016 E. L.	May 17, 1921	63	60.5	37	18	1,650,000	3,700	3800	63	4635	77
	May 19, 1921	M.	..	40	20	2,150,000	7,000	3800	63	4740	79
A314129 G.	June 6, 1921	53 M.	52	36	16	1,480,000	1,200	3265	62	3875	74
A360350 F. U.	June 18, 1921	45 F.	40	44	17	1,340,000	4,000	2965	74	3575	89

Chronic Anemia. This group includes 12 cases of pernicious anemia, one of severe secondary anemia and one of Banti's disease (Tables 1 and 2). In 6 cases of pernicious anemia the values for plasma volume were high, ranging from 66 to 81 cc for each kilogram of body weight. The corresponding values for blood volume were

77 to 106 cc for each kilogram; only two patients had a blood volume above normal. In general, the highest plasma values were in patients with low hemoglobin percentages, although no absolute relationship could be demonstrated. The highest plasma volume, 81 cc for each kilogram, calculated on the basis of cubic centimeters of plasma to body weight was found in Case S. B., when the hemoglobin was 41 per cent. In several patients changes in the hemoglobin percentages were associated with definite variations in plasma volume. In Case W. R. (Chart 1) the rise in hemoglobin from 23 to 88 per cent, an increase in weight of 5 kg., and general clinical

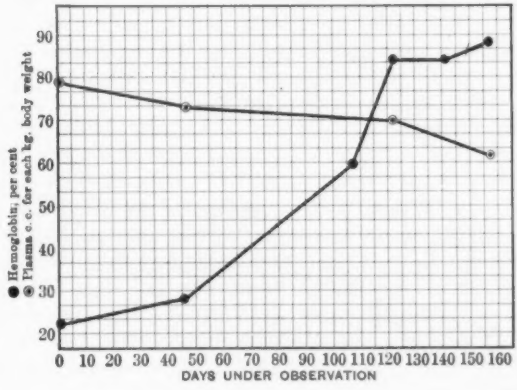

CHART I

improvement were associated with a definite decrease in plasma, 78 to 62 cc for each kilogram. A similar though smaller decrease in plasma was observed in Case C. H. P. with a distinct rise in the hemoglobin percentage. The converse findings were observed in Case R. G., a fall in hemoglobin, 47 to 26 per cent, being accompanied by an increase in plasma, 60 to 69 cc for each kilogram. Smith made repeated blood-volume determinations in a single case of pernicious anemia using the carbon monoxid method. He noted that the blood volume increased as the hemoglobin percentage fell. In the remaining 6 cases of the series of pernicious anemia the plasma volume varied from 52 to 63 cc for each kilogram and the blood volume from 64 to 82 cc for each kilogram. The findings in the last 6 cases are similar to the findings Bock noted in his series of 7 cases of pernicious anemia.

Two volume determinations made within a month in the case of Banti's disease (Case L. J., Table 2), gave practically identical results. The secondary anemia was not marked and the patient was up and around. Both the plasma and blood volumes were distinctly increased. In the last case (Case H.) the patient was

suffering from severe secondary anemia, the hemoglobin being 20 per cent. The amount of plasma, 60 cc for each kilogram, was not strikingly increased, while the total amount of blood, 69 cc for each kilogram, was low.

TABLE 2.—SECONDARY ANEMIA.

Case.	Date.	Age and sex.	Weight, kg.	Hemoglobin, per cent.	Hematocrit, erythrocytes, per cent.	Erythrocytes.	Leukocytes.	Plasma, cc.	Plasma, cc, for each kg.	Blood, cc.	Blood, cc, for each kg.
26850 L. J.	Nov. 12, 1919	27	..	65	..	3,400,000	7800				
Banti's disease	Dec. 4, 1919	M.	57	71	26.4	...	..	4115	72	5605	98
	Dec. 29, 1919	..	55	..	26.4	...	..	4000	73	5435	99
H.	Dec. 10, 1919	M.	70	17	10.0	..	..	4250	61	4700	67
Secondary anemia	Dec. 20, 1919	..	70	20	14.0	...	..	4210	60	4880	69

In pernicious anemia great variations in the blood volume have been reported. Smith used the carbon monoxid method and found that the blood volume in this disease might be increased or decreased below the normal level. In one case variations in volume were presented which bore a definite relation to changes in the clinical course of the disease. Such results may possibly be explained by plasma volume changes as noted in the present series. Quincke, Lindeman, and Denny (Table 4) have determined the blood volume in pernicious anemia by methods based on the concentration of the red blood corpuscles before and after transfusion. The findings noted by Lindeman are open to criticism as he reports some exceedingly low values, much lower than those of other observers. The varied results of both Lindeman and Denny may not be due so much to technical inaccuracies inherent in the methods themselves as to the uncertain fate or distribution of the normal cells after their introduction into the circulation of a diseased person.

The fact that Bock, who used the dye method, failed to find in 7 cases of pernicious anemia a single plasma volume above the normal, may possibly be explained by mere chance or by the clinical condition of the patients at the time the estimations were made. As I have noted, in only one-half of the present series of cases was the amount of plasma increased, while in the other half the findings were practically within normal limits. The high plasma content often found in this study would lead one to the conclusion that in chronic anemia the variations in plasma volume are much greater in latitude than in the normal person. The exact significance of this increase is difficult to ascertain. We know that following

acute hemorrhage, with considerable loss of erythrocytes, the depleted circulation can be readily augmented by an increase in the plasma fraction due to an inflow of fluid from the tissues. Thus, the total circulating volume of blood becomes adequate by a relative increase in the plasma volume. The subsequent increase in blood volume to the normal level is brought about by the rapidly increasing number of erythrocytes. This early mechanism of a rapid inflow of fluid into the circulation after hemorrhage may fail because of the lack of tissue fluid, or inability of the smaller vessels to take up fluid, even when present in sufficient amount. Such a condition was found in cases of hemorrhage associated with traumatic shock. Now, early in a slowly progressing anemia the usual mechanism for maintaining an adequate blood volume may be called into play with a resulting high plasma content. Since the subsequent increase in erythrocytes does not occur, however, the total blood volume is reduced. In order, then, to maintain a normal or high blood volume in such cases there must necessarily be an increased plasma content. The actual proof in certain cases in this study of a high plasma volume would indicate the possibility of such a reaction. There is often a tendency to hemorrhage in chronic anemia. This may be a possible factor in causing variations in plasma volume.

Chronic Leukemia. Is the dye taken up by the leukocytes in leukemic blood? If this occurred to any extent the increased dilution of the dye would give estimations of plasma volume much too great. It had previously been demonstrated *in vitro* that little or none of the dye is taken up by the erythrocytes or leukocytes in normal blood. This observation was confirmed by Harris. A similar experiment was carried out on leukemic blood. This consisted in adding a known amount of dye to equal quantities of whole leukemic blood and plasma.

In Case J. F. (Table 3), November 28, 1919, the total leukocyte count was 44,000 for each cubic millimeter. December 2, two samples of blood were rendered incoagulable by 0.1 gm. of sodium citrate[4] and 0.01 gm. of sodium oxalate. The tube containing the oxalated blood was centrifugalized and the plasma pipetted off. To Tube "A," containing 8 cc of citrated whole blood, was added from an accurately graduated 1 cc pipette, 0.03 cc of a 1.5 per cent solution of vital red. The tube was gently shaken for eight minutes in order to insure a thorough mixing of the dye and blood. To Tube "B" containing 8 cc of oxalated plasma was also added 0.03 cc of a 1.5 per cent solution of vital red. After Tube "A" was centrifugalized[5] and the hematocrit reading taken, the plasma was pipetted off and compared in a Duboscq colorimeter with the plasma dye mixture from Tube "B." The readings were $\frac{A}{B} = \frac{7.0}{9.0}$. Therefore, Tube

[4] Sodium citrate was used as anticoagulent because in this amount it has no toxic action.

[5] Three thousand revolutions each minute for twenty minutes.

TABLE 3.—CHRONIC LEUKEMIA.

SPLENOMYELOGENOUS.

Case.		Date.	Age.	Sex.	Weight, kg.	Height, cm.	Hemoglobin, per cent.	Hematocrit, erythrocytes and leukocytes, per cent.	Erythrocytes.	Leukocytes.	Plasma, cc.	Plasma, cc. for each kg.	Plasma, liters, for each sq. m.	Blood, cc.	Blood, cc. for each kg.	Blood, liters for each sq. m.	Basal metabolic rate, per cent.
26828	J. F.	Sept. 17, 1919	44	M.	..	..	50	..	2,600,000	326,000							
		Oct. 15, 1919	..	..	..	..	45										
		Oct. 24, 1919	..	..	..	..	..	..	1,728,000	153,000							
		Nov. 4, 1919	..	..	..	..	..	..	...	..	..	..	..	..	..	..	+57
		Nov. 8, 1919[1]	..	..	..	..	20	..	896,000	230,000							
		Nov. 18, 1919	..	..	64	181	47	22	1,888,000	..	5000	77	2.74	6400	100	3.52	
		Nov. 26, 1919	..	..	65	..	59	28	2,513,000	45,000	5710	88	3.12	8000	123	4.37	
		Dec. 2, 1919[2]															
		Dec. 7, 1919	..	..	..	..	..	..	2,911,000	46,000							
		Dec. 19, 1919	..	..	67	..	68	30	3,040,000	9,200	5405	80	2.90	7720	115	4.17	
		Jan. 13, 1920	..	..	71	..	74	32	4,100,000	96,000	4820	67	2.64	7090	100	3.73	
		Feb. 27, 1920	..	..	..	..	81	39	...	32,000	4705	..	..	7715			
		Mar. 19, 1920	..	..	..	..	..	..	...	..	..	..	..	..	..	..	+43
A175501	A. T.	Mar. 4, 1921	43	F.	51	150	91	41	...	..	3345	65	2.32	5670	111	3.93	+36
		May 18, 1921	..	..	..	..	..	..	3,980,000	135,600							
A186558	H. A. S.	Mar. 17, 1921	55	F.	51	161	71	43	2,660,000	176,000	3050	60	2.05	5360	105	3.55	+37
A273047	A. K.	Mar. 18, 1921	49	M.	68	175	71	37	2,640,000	177,000	4580	67	2.53	7270	107	4.01	+36
A356322	C. C. K.	May 9, 1921	18	M.	56	169	46	26	2,210,000	97,000	3975	70	2.42	5370	96	3.29	+44
		May 13, 1921	..	..	56	..	46	27	2,110,000	156,000	3925	70	2.42	5375	96	3.29	+47
A315316	J. S.	May 10, 1921	30	F.	53	156	48	47	2,700,000	514,000	3680	69	2.50	6945	131	4.63	+59
								LYMPHATIC.									
A355667	C. S.	April 21, 1921	50	F.	56.6	159	79	43	3,590,000	394,000	2910	51	1.87	5105	90	3.27	+51
A354070	W. C.	April 22, 1921	55	M.	61	172	87	40	5,010,000	88,000	4195	68	2.44	6990	114	4.06	+ 9
A342995	H. T.	April 22, 1921	66	M.	71	165	88	38	4,760,000	87,000	3845	54	2.18	6200	87	3.50	+44
A258636	J. H. K.	May 25, 1921	61	M.	55.5	169	76	42	4,100,000	112,000	3295	57	2.02	5590	102	3.44	+12

[1] Severe internal hemorrhage, esophageal (?)

[2] Experiment *in vitro* in regard to dye being taken up by the leukocytes.

"A" contained 128.6 per cent as much dye for each cubic centimeter as Tube "B." The amount of plasma in the blood in Tube "A" as shown by the hematocrit was 6.15 cc. Thus, if 0.03 cc of dye is diluted in 6.15 cc of plasma, 1 cc of dye is diluted in 205 cc of plasma. In Tube "B" 0.03 cc of dye is diluted in 8 cc of plasma, thus 1 cc of dye is diluted in 266 cc of plasma. Therefore, there should be $\frac{266}{205}$ or 129.7 per cent of dye in Tube "A." Colorimeter reading, as calculated from hematocrit data, was 129.7 per cent. Colorimeter reading observed was 128.6 per cent.

In the foregoing experiment the calculated and observed values agree so closely that the amount of dye lost from the plasma must be negligible. This experiment is offered as evidence that the leukocytes in splenomyelogenous leukemia have no special tendency, during the short period of a blood-volume determination, to take up the dye, vital red, from the circulating plasma.

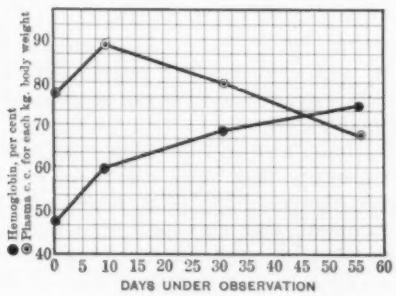

CHART II

In 10 cases of chronic leukemia (Table III), 6 were splenomyelogenous and 4 lymphatic in type. Each showed considerable variation in the plasma and blood-volumes, although the most marked changes occurred in the cases of splenomyelogenous leukemia. No exact relation between plasma volume, hemoglobin percentage or leukocyte count was noted. Detailed studies in Case J. F. are of interest: following a severe internal hemorrhage, probably esophageal in origin, the patient's hemoglobin fell to 20 per cent. Ten days later, with the hemoglobin at 47 per cent, the plasma and blood volume were definitely high, the plasma amounting to 77 cc for each kilogram. The patient continued to improve rapidly and on the next examination, within nine days, the hemoglobin rose to 59 per cent while the plasma volume reached the very high mark of 88 cc for each kilogram. On three subsequent determinations the plasma volume showed a gradual decrease, while the hemoglobin percentage rose from 59 to 81 (Chart 2). During this period of rapid recovery, the patient received several roentgen-ray treatments and as a result the leukocyte count on one occasion

fell to 9200. The total blood volume remained consistently high, 100 to 123 cc for each kilogram, during the entire period of observation, November 18, 1919, to February 27, 1920.

In Case C. C. K., two determinations made within a few days gave almost identical results. Here again both the plasma and total blood were increased. In the 4 other cases the plasma amounted to from 60 to 69 cc for each kilogram, while the blood volume varied between 105 and 131 cc for each kilogram. The striking feature, therefore, in these cases is the consistently high plasma volume.

In considering the data of the 4 cases of chronic lymphatic leukemia there was only 1 case (Case W. C.) in which the plasma volume was noticeably increased. The amounts of plasma observed in Cases C. S., H. T., and J. H. K., were within normal limits.

The basal metabolic rate was determined in all of the 10 cases of leukemia. In the splenomyelogenous group the rates were all definitely elevated. On the other hand, in cases of lymphatic type, two were raised while two had rates of +9 and +12. The highest plasma volume, 68 cc for each kilogram, was in Case W. C., with the rate of + 9. No absolute relationship, therefore, was found to exist in this small series between plasma or blood volumes and the basal metabolic rates.

Clinicians have long believed that certain cases of leukemia are plethoric. The presence of a large volume of circulating leukocytes also suggests the possibility of an increased total volume of blood. That the leukocytes may possibly play such a part is supported by frequent high cell volumes obtained *in vitro* in the hematocrit tube (Table 3). Few actual blood-volume determinations have been made in leukemia.

Plesch and Oerum each report a single case having a normal blood volume. Kammerer and Waldmann, using the Behring tetanus antitoxin method, made determinations on 4 cases, two lymphatic and two splenomyelogenous in type. In one of the latter the blood volume was high. Behring also reports the finding of an increased volume in 2 cases of leukemia (Table 4). The results recorded in this series indicate that in certain cases the plasma volume is high and that this is more often associated with an increased blood volume than in chronic anemia. It is difficult to correlate the large amount of plasma with any one other clinical or laboratory finding common to the disease. The enlarged spleen and liver were considered as possibly having a casual relation. This idea was given added support because of the finding of a large plasma volume in the case of Banti's disease (Case L. J., Table 2). Giffin and Haines are at present making determinations before and subsequent to splenectomy in such cases. If a previous high plasma volume should still persist after splenectomy, then the enlarged spleen could be definitely ruled out as an etiologic

factor. The relation of an enlarged liver to a high plasma content is obviously more difficult to appraise.

TABLE 4.—PREVIOUS DETERMINATIONS IN PERNICIOUS ANEMIA AND CHRONIC LEUKEMIA.

Author.	Method.	Cases.	Plasma, cc. for each kg., extremes.	Blood, cc. for each kg., extremes.	Blood, per cent of body weight, extremes.	Remarks.
PERNICIOUS ANEMIA.						
Smith . . .	Carbon monoxid	7	. . .	49—117	4.9—11.7	
Oerum . . .	Carbon monoxid	1	. . .	. . .	5.1	
Plesch . . .	Saline infusion	1	. . .	37.5	3.96	
Behring . . .	Tetanus antitoxin	2	. . .	. . .	9.6—11.7	
Quincke . . .	Erythrocytes before and after transfusion	2	. . .	. . .	4.3— 5.0	
Lindeman . .	Hematocrit before and after transfusion	11	. . .	26—60	2.4— 5.8	
Denny . . .	Oxygen capacity of blood before and after transfusion	10	. . .	. . .	5.1— 9.7	
Keith, Rowntree and Geraghty .	Vital red	2	54—72	66—81	7.0— 8.7	
Bock	Vital red	7	38—59	44—72	4.3— 7.3	
		LEUKEMIA.				
Plesch . . .	Saline infusion	1	. . .	51.6	5.4	Type of leukemia (?)
Behring . . .	Tetanus antitoxin	2	. . .	. . .	10.5—11.5	Type of leukemia (?)
Kammerer and Waldemann .	Tetanus antitoxin	2	. . .	83—86	8.7— 9	Lymphatic leukemia.
	Tetanus antitoxin	2	. . .	93—110	9.7—11.5	Myelogenous leukemia.

Summary. 1. Wide variations in blood and plasma volume have been observed in 24 patients presenting definite evidence of chronic disease of the blood-forming organs. These variations were sometimes noted in the same patient.

2. In certain cases of chronic anemia there was a striking increase in the volume of plasma; in others, a normal plasma volume. In all cases the blood volume was normal or reduced.

3. In cases of chronic anemia no exact relationship could be determined between the amount of plasma and the hemoglobin percentage, although in individual cases these varied somewhat inversely with one another.

4. An experiment *in vitro* on the blood of a patient with splenomyelogenous leukemia failed to show that any appreciable amount of the dye, vital red, is taken up by the leukocytes.

5. In chronic leukemia the blood volume is almost invariably increased. The plasma volume often reaches a high value, especially in the splenomyelogenous type.

6. In chronic leukemia no definite relationship could be demonstrated between the basal metabolic rate and the variations in blood or plasma volume.

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A CASE OF MULTIPLE MYELOMA.

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Inasmuch as cases of multiple myeloma are still uncommon, this one has been reported. For the opportunity of so doing, thanks

are due to Dr. Paryzek and to the residents and interns under whose care the patient came. When compared with the others that have been reported, this particular one is interesting in that it is so thoroughly typical of the classic form.

CASE REPORT.—Patient I. N., colored man, aged forty-nine years. Admitted to the Cleveland City Hospital the first time on January 9, 1921, when the following notes were obtained:

Previous History. Born in Mississippi. Influenza two years ago. Chancre thirty years ago and also one attack of gonorrhea. Had "chills and fever" once or twice a year until 1919. He claimed to have had night-sweats for the past eight to ten years, but no hemoptysis or loss of weight. No skin lesions or sore-throat. No loss of power in the extremities.

Present Illness. Began December 12, 1920, when the patient had to go to bed on account of severe precordial pains which radiated through the chest and were made worse by exertion. Remained in bed practically all the time. Finally brought to the hospital in January, 1921. On admission his chief complaint was that he felt "sore all over," but particularly throughout the abdomen and in the lumbar region.

Physical Examination. No cough; marked hoarseness. Holds chest rigid and breathes with difficulty. Movement is distinctly painful, but by moving very slowly and carefully is able to change his position.

Ear, nose and head showed nothing abnormal. Pupils slightly unequal and irregular and reacted sluggishly to light. Teeth in good condition. Mucous membranes appeared normal. No glandular enlargement in the neck. Jugular vessels slightly distended. Slight tracheal tug. Chest is flattened abnormally in its anteroposterior dimension. The sternum is not perfectly straight, is unduly flexible, particularly at the junction of the manubrium and the gladiolus, at which point there is a moderately soft mass about 2.5 cm. in diameter. Ribs also are unduly flexible and show many small, round or oval areas in which the bone is quite soft. (These softened areas are quite tender to pressure.) Many small nodules, apparently subperiosteal, are found.

Both clavicles are somewhat enlarged, particularly in the middle third, where they are quite soft and where a crackling sensation is noted on pressure. In these areas no solid bone can be felt, and there is evidently a lack of support to the shoulder girdle. The acromion processes on both sides show a very similar condition, and in the left scapula there is a large tumor mass that is comparatively safe.

Lungs resonant throughout. Breath sounds normal.

Heart: Diffuse visible precordial activity to right and left of the sternum. Systolic thrill palpable over apex and aortic area.

The sounds at the apex are accompanied by a systolic murmur heard best at the aortic area. Aortic second sound increased. Pulse rate, 90; good rhythm and volume. Arteries tortuous.

Abdomen: Slight tenderness of the liver, which extends three finger-breadths below the costal margin. Spleen not palpable.

External genitalia: Negative. No enlargement of the prostate.

Extremities: Show nothing abnormal.

Neurological: Reflexes normally active. No Babinsky, clonus or ataxia. No sensory changes. No lesions of the cranial nerves.

Blood: Red blood cells, 4,720,000; white blood cells, 7200; hemoglobin, 80 per cent; polynuclears, 58; small, 30; large, 7; transitionals, 5; myelocytes, 0.

Blood-pressure: Systolic, 175; diastolic, 100.

Spinal fluid: Clear. Increased pressure. 20 cc obtained. Globulin present. Ten cells present; mononuclear.

Wassermann negative with both blood and spinal fluid.

Lange colloidal gold test negative.

Temperature: Lowest, 36°; highest, 37.4°.

Pulse: Lowest, 70; highest, 102.

Respiration: Lowest, 18; highest, 25.

Urine, January 24, 1921: 1008. Albumin present. Sugar, 0. A few casts. Bence-Jones protein positive.

January 26 1921: 1008. Albumin present. Sugar, 0. No casts. Bence-Jones protein positive.

Roentgen-ray report, January 26, 1921: Marked dilatation of the aorta with transverse position of the heart. Multiple areas of destruction of bones; most marked in ribs and clavicles, the anterior portion of the ribs being almost completely destroyed as far as the bony structure is concerned. There is also considerable involvement of the scapulæ, upper portion of the humeri, upper spine and skull. Of the skull the bones that show the most involvement are the parietal, frontal and malar. Also some involvement of the lower jaw and a few small areas in the femurs.

After remaining a few weeks in the hospital the patient felt better and decided to return home. His improvement continued to some extent and he attempted to work, but the old symptoms reappeared and he had to go back to bed.

The patient was readmitted to the hospital on July 7, 1921. At this time his condition was distinctly worse. The palpable nodules were more numerous and larger. Softened areas were present in the skull; the sacrum on the right side was thickened and the head of the right femur was distinctly enlarged but not softened. No enlargement of the lymph nodes was found.

Blood, July 6, 1921: White blood cells, 7000; hemoglobin, 85.

July 17, 1921: Polynuclears, 63; small, 22; large, 8; transitionals, 3; myelocytes, 4.

July 18, 1921: Red blood cells, 3,900,000; white blood cells, 7800; hemoglobin, 68.

FIG. 1.—Roentgen-ray of skull showing many areas of softening.

Blood-pressure: Systolic, 190; diastolic, 100.
Urine, July 7, 1921: Casts, +; sugar, 0; specific gravity, 1011.
July 13, 1921: Albumin, ++; casts, ++.

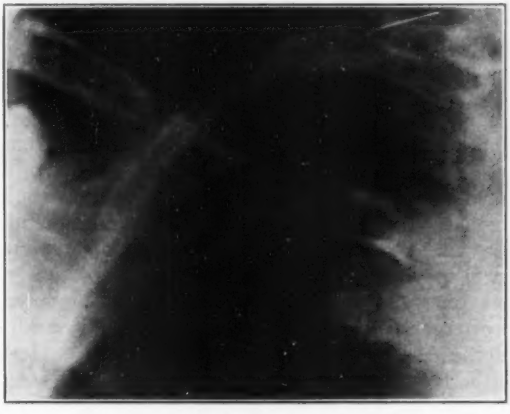

FIG. 2.—Roentgen-ray of right clavicle and ribs showing involvement.

July 18, 1921: Albumin, ++; casts, +.
July 19, 1921: Albumin, +++; casts, +.

Bence-Jones protein: large amount present constantly.

Feces and spinal fluid were not examined.

Blood Wassermann negative.

On August 26 he died, but unfortunately no relative could be located in order that a permit for an autopsy could be obtained until the following day, when it was performed twenty-nine hours after death.

I. N. (autopsy twenty-nine hours after death).

Clinical Diagnosis. Multiple myeloma. Chronic aortitis with dilatation and elongation of ascending portion of the arch. Generalized arteriosclerosis. Cardiac hypertrophy.

Anatomical Diagnosis. Multiple myeloma. Bronchopneumonia, bilateral. Edema of the lungs. Chronic parenchymatous nephritis with acute changes. Mesenteric adenitis, tuberculous. Atheroma of the aorta.

Body that of a much emaciated adult negro of about fifty years of age. Slight rigor. The chief peculiarity lies in the condition of the bones. There evidently has developed a growth within the marrow cavities causing an atrophy of the bony tissue with softening and in some cases fracture of the bone. This is particularly noticeable in both clavicles, which are much enlarged in their middle portions, crackly to the touch and no longer continuous. Similar conditions were present in the upper portion of the sternum and in many of the ribs, several of the latter showing multiple lesions. In the skull several small areas of softening were present. The upper portions of the two humeri were distinctly enlarged, as was the upper portion of the right femur. No areas of softening were noticed in the above long bones.

On opening into the canal of the left humerus the marrow was a dark-brownish red and very soft. Apparently no definite structure.

No change was found in the marrow of the right tibia.

On incising the masses found in the sternum and in the ribs they were found to be quite soft, pale gray, with numerous minute areas of congestion or hemorrhage. They appeared to be distinctly encapsulated by a thin membrane which was probably the stretched periosteum. No fragments of bone were found within the tissue. The impression was that of a central mass undergoing expansile growth with subsequent atrophy of the surrounding bone. According to the autopsy findings the following bones were involved: skull, cervical vertebræ, both scapulæ, both clavicles, sternum, most if not all of the ribs, both humeri, both iliac bones and the upper portion of both femurs, particularly the right. The forearms and hands, legs and feet showed no changes.

With the exception of several of the mesenteric, there was no enlargement of the lymph nodes in general nor metastatic growths in any of the organs.

Microscopic Diagnosis. Myeloma of bone-marrow of the humerus, of the rib and of the sternum. Fibrous myocarditis with calcification in the walls of the vessels. Emphysema and congestion of the lungs with extensive calcification of the alveolar walls. Chronic interstitial nephritis with extensive calcification. Pigmentation, congestion and calcification in the spleen. Slight calcification in the pancreas. Cloudy swelling of the liver. Fibrous tuberculosis of the mesenteric lymph node.

Heart: Distinct calcification of the elastic membrane of the larger arteries accompanied by degenerative changes of the subintimal tissues. One portion shows a very extensive replacement of muscle fibers by large masses of dense connective tissue. In these masses are many particles of lime, as evidenced by the irregularity of outline and deep staining by hematoxylin. Capillaries filled with blood.

FIG. 3.—Heart showing deposits of lime.

Lung: The conspicuous feature is the very widespread calcification of the alveolar capillary vessels. In many instances the wall has been replaced by a large mass of lime salts in which no remnants of tissue are visible. Fragments are found occasionally lying within the alveoli, possibly misplacements due to the cutting of the tissues. The walls of the larger bloodvessels also show similar infiltration. In some areas there is tremendous congestion with the escape of blood into the alveoli.

Kidneys: Very great loss of tubules with replacement by a very marked widespread formation of dense fibrous tissue. Many of the glomerular tufts have undergone fibrous changes as a result apparently of capsular proliferation. Widespread infiltration by lymphocytes. Numerous tubules contain hyaline material. Some

thickening of the bloodvessel walls but no calcification. In the fibrotic areas of the cortex particularly there is a widespread calcification, masses lying not only in the connective tissue but within the tubules as well.

Adrenal: Shows no definite lesion other than an area in which there are numerous small masses of rather large cells containing round or oval, deeply staining nuclei, surrounded by a distinct zone of protoplasm. No calcification.

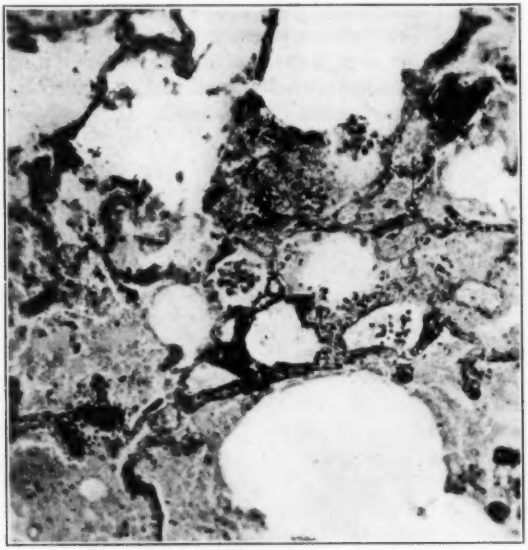

FIG. 4.—Lung showing deposits of lime in the alveolar walls.

Liver: Epithelium swollen and cloudy. Blood sinuses distended. No cellular infiltration. No calcification.

Spleen: Large masses of lime salts in the walls of the large bloodvessels. Some pigmentation and congestion.

Pancreas: Epithelial changes, probably postmortem. Some very slight calcification in the walls of a few of the large vessels.

Mesenteric lymph nodes: Show many irregular areas of fibrosis with some necrosis in which are many typical Langhans giant cells. No calcification.

Lymph node: Shows a very distinct fibrosis but no areas of degeneration or giant-cell formation. Apparently a chronic fibrosis. No calcification.

Marrow (from the left humerus): Section shows two very distinct types of tissue. One of them is composed of broad bands of homogeneous material, suggesting degenerated fatty tissue, the

meshes of which are engorged with blood. Practically no white cells are present in the above area. There is then a very abrupt change into an area in which there are myriads of white cells and very few erythrocytes. These cells occupy the blood spaces and enclose round clear spots evidently where fat has been dissolved out. Under the oil-immersion two types of large cells are found to predominate. In one the nucleus is round or slightly oval, stains quite deeply and is surrounded by a narrow but distinct zone of cloudy but nongranular protoplasm that stains a very faint blue. In the second type the nucleus is distinctly larger, contains much less chromatin and consequently does not stain so deeply; is very definitely vesicular. It is surrounded by a large amount of protoplasm, which although nongranular appears distinctly cloudy. In many instances the nuclei are eccentrically situated in the cell.

Although the majority of the cells conform to these two types there are many variations. There are very large cells with very densely staining nuclei and there are many small cells with vesicular nuclei. Throughout the tissue are many large mononuclear cells with a granular eosinophilic protoplasm. Here and there are found multinucleated cells many times larger than the surrounding cells, conforming to the characteristics of the megakaryocyte. No mitotic figures noted.

Tumor from rib: The tumor mass is sharply delimited by a definite band of connective tissue which probably is the result of condensation. Beyond this is muscle tissue which in a few places shows infiltration by the tumor cells. Throughout the section are many very minute capillaries, all of which show a complete endothelial wall. There are no places in which blood spaces, formed by the cells themselves, were noted, an arrangement that explains the absence of metastasis.

Under the oil-immersion it is quite evident that the two varieties of cells already mentioned are but variations of one type.

The cells are large and more or less polygonal as a result of mutual pressure; the nuclei, as a rule, are eccentrically placed in a large amount of a cloudy but nongranular protoplasm. The nuclei differ greatly in their staining. As a rule the smaller ones stain the more deeply. As they become larger there appears to be less chromatin, but what is present is arranged mainly in small irregular masses around the periphery of the nucleus, leaving a comparatively clear central area.

In many cells the nucleus has definitely broken down into small fragments, and there are others in which no trace of the nucleus can be seen.

An occasional granular eosinophilic mononuclear cell is found and some show a definitely pinkish protoplasm, but no granules are evident. No typical megakaryocytes were found, although there were a few cells with two or three nuclei, but their characteristics

were those of the tumor cell. No definite fibrils could be distinguished between the individual cells.

Tumor from the sternum in every respect appeared similar to that from the rib.

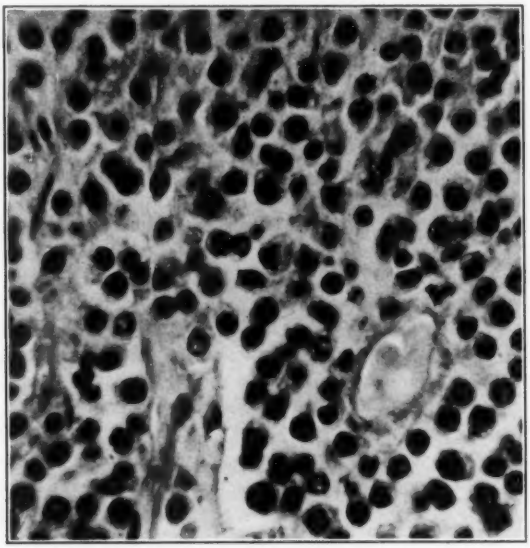

FIG. 5.—Tumor mass from the sternum. Oil-immersion.

From the morphologist's point of view the interesting feature of these tumors is the origin of the cells composing them. A classification based entirely on morphology is very unreliable, yet many observers who have reported such cases have considered them as "plasma-cell" tumors on account of their resemblance to that cell. Others classify them as atypical derivatives from the neutrophilic myelocytes. That they originate primarily within the bone-marrow seems to be undisputed, as examinations of the tissues and blood in these cases show no source outside of the marrow, although in a very few instances myelocytes have been found in the blood stream. All the evidence tends, however, to show that the multiple myeloma is a disease that occurs *de novo* in the marrow and is not an instance of metastases from some single primary tumor.

According to most hematologists the parent cell in the bone-marrow is the myeloblast; from it both the leukocytes and the erythrocytes develop. Although the myeloblast is nongranular its descendants are the granular myelocytes and polymorphonuclear leukocytes. The plasma cell, on the other hand, is supposed to be derived from the nongranular lymphocyte, which is not con-

sidered to originate within the bone-marrow. Although there is a certain similarity between the myeloma cell and the plasma cell the resemblance may not be very striking. The tumor cell is distinctly larger, there are great variations in the size and staining reactions of the nuclei, and the protoplasm, although seldom granular, is definitely cloudy and takes a neutrophilic tinge.

Vance[1] in discussing multiple myeloma states: "There is no doubt, however, that these cells, diverse as they are, are derivatives of the undifferentiated cell of the bone-marrow or myeloblast, which is the ancestor of both the leukocyte and the erythrocyte." He holds that the cells in his case all took their origin from the cells in the bone-marrow, although the oxydase test was negative.

Forman and Warren[2] say that "Since it has been established definitely that the oxydase reaction is characteristic of myeloid cells the application of this reaction to the cells of a myeloma ought to be of great service in identifying these tumors." In the case they report they used this method and found oxydase granules not only in cells morphologically like the myeloid type but also in many of the cells which in size, shape and staining closely resembled the plasma cell. Although most of the cells gave the reaction there were some that did not. The question arose, therefore, as to whether or not such cells had matured sufficiently to contain the granules.

Beck and McCleary[3] found in their case that the indophenol blue test showed oxydase granules, thus indicating that the cells belonged to the myeloid group, although the morphology was that of the plasma cell. Jacobson[4] reports a case of "multiple myeloma of the plasma cell, nongranular, nonoxydase type."

Mallory[5] states quite emphatically where the myeloma cell does not belong but does not classify it. "The type cell of this tumor has not yet been determined. Evidently it does not belong to the myeloblast series of cells because it does not differentiate like them. Moreover the myeloma is never associated with myelogenous leukemia. The only other cells peculiar to the bone-marrow are the erythroblast and the megakaryocyte. Possibly it arises from one of these cells. It is claimed by some writers that there exists in the bone-marrow another peculiar kind of cell which they call the bone-marrow plasma cells, and that from it this tumor arises. Time alone will tell." Mallory makes no mention of the oxydase reaction as a method of determining the myeloid origin of the cell.

MacCallum[6] divides the myelomas into two kinds: One composed

[1] Am. Jour. Med. Sci., 1916, **152**, 693.
[2] Jour. Cancer Research, 1917, **2**, 79.
[3] Jour. Am. Med. Assn., 1919, **72**, 480.
[4] Jour. Urology, April, 1917.
[5] Pathologic Histology, 1914, p. 338.
[6] Pathology, 1916, p. 775.

of lymphoid cells and another composed of myeloid cells. In the former the "cells are nongranular, mononuclear, have a basophilic protoplasm and are very similar to the plasma cell, with which they are regarded by most writers as identical." In the second type the cells correspond with the myeloblast.

Ewing[7] in classifying myeloma according to different observers gives four groups: (1) Plasmocytoma; (2) erythroblastoma; (3) myelocytoma, adult and embryonal; (4) lymphocytoma. "Whether such varied interests are actually represented in the scope of multiple myeloma or whether we have to deal with varying grades of anaplasia in a single cell or origin remains to be determined. At present the data seem to favor the former alternative."

Hoping that some definite information might be obtained by means of the oxydase reaction, portions of two tumor masses which had been hardened in formalin were frozen, sections made and stained according to the method given by Forman and Warren.[8] Although the reaction took place no definite conclusion could be drawn because only a very small percentage of the cells showed blue granules. Scattered through the tumor tissue were granular cells occurring either singly or in small masses, intimately intermingled with other cells which showed no reaction. There were also many large areas in which none of the cells reacted. In order to bring out the nuclear structure, safranin was used as a counterstain and proved to be very satisfactory, but no definite differences could be determined between those cells giving the oxydase reaction and those that did not. Examinations made of the sections stained by eosin and hematoxylin revealed no areas in which the cells differed distinctly from neighboring groups.

There would seem to be several explanations as to why such a condition should exist. As several observers have suggested it may be that the great majority of the cells, although myelogenous in origin, had not reached that point of development in which granules appear. It is a well-recognized fact that the connective-tissue tumors may represent all the different stages of development and that they remain in that particular stage. A round-cell sarcoma does not eventually become of the spindle-cell type. In the myeloma we are dealing with tumors of varying degrees of malignancy. In those in which practically all the cells contain oxydase granules the development may have been more complete than in those which show little or no reaction.

Although we know that the myeloma develops within the bone-marrow, nothing is known as to the fate of the original marrow cells. It could be assumed that many of them remain more or less physiologically active in spite of being imbedded in masses of tumor cells. In this case scattered cells and cell groups might be considered as

[7] Neoplastic Diseases, 1919, p. 289.
[8] Loc. cit.

remnants of the original tissue, consequently the fact that some of the cells contain blue granules and others do not has little bearing as to the origin of the non-reacting cells. As there were no metastases in this case there was no way of determining whether or not the granular cells were actually neoplastic or not.

From the morphologic viewpoint the cells in this tumor resemble plasma cells much more closely than any other type. It being accepted rather generally that the plasma cell is a derivative of the nongranular lymphocyte, such growths, therefore, would have to be considered as lymphatic in origin, but histologists do not consider the bone-marrow as playing a part in the formation of lymphocytes. Such being the case it does not seem permissible to consider any of the primary myelomas as being either true plasma cell or lymphocytic tumors.

Accepting the view that we are dealing with anaplastic stages of a single cell, the oxydase reaction becomes nothing more than a method of determining the stage of development of any particular myeloma. By analogy to the sarcoma the earlier the stage the more malignant. It would be interesting if comparisons could be made in this respect between various cases.

An interesting feature in the case here reported is the presence of lime deposits in the heart, lungs, kidneys, spleen and pancreas. As a result of the expansile growth of the individual tumor masses there occurs a great destruction of the bone which causes a large amount of lime salts to be set free. These salts are carried through circulation and deposited in the different organs, particularly in the walls of the vessels. In the lung there were large areas in which the alveolar walls were represented by a network of lime deposit.

Vance[9] gives references to three cases in which deposits of calcium were found in the viscera.[10]

Blatherwick,[11] as a result of his chemical investigations of a case of myeloma, reports that the analyses of the feces and urine showed an abnormally increased calcium excretion.

From the clinical side there is nothing unusual in this case, excepting possibly its being a colored man. As in the majority of instances the patient was about fifty years old. There was nothing suggestive in the previous history as far as any etiologic factor was concerned. The initial lesions in the ribs, clavicle and sternum, with subsequent involvement of more distant bones, is typical, and the duration of the disease, eight months, is rather characteristic, as it seems to be unusual for a patient to live more than about one year after the appearance of symptoms.

[9] Loc. cit.

[10] Bender: Deut. Zeit. f. Chir., 1902, **65**. Scheele and Herxheimer: Zeit. f. klin. Med., 1904, **54**. Tschislowitsch and Kolesnikoff: Virchows Arch., 1909, **197**.

[11] Am. Jour. Med. Sci., 1916, **151**, 432.

ON OCCUPATIONAL SENSITIZATION TO THE CASTOR BEAN.

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The literature affords numerous examples of poisoning with the castor bean and with its products. Thus the toxic action resulting from the ingestion of the whole bean, accidental or otherwise, and even from the medicinal use of castor oil has been recorded. Especially noteworthy is the toxalbumin found in the residue of the castor beans after the removal of the oil. Stillmark, in 1889, named this toxalbumin "ricin" and regarded it as a globulin. Osborne, Mendel, and Harris,[1] however, have ascribed the toxic action of the castor bean to the protein fraction which is an albumin, coagulable at 60° to 70.° Ricin ranks among the most powerful of the vegetable poisons when injected directly into the bloodstream. It, also, has the property of agglutinating red blood cells extravascularly. Injected subcutaneously into rabbits, ricin proves fatal in a dose of 0.0005 mg. per kilogram of body weight. At the point of injection, a localized area of necrosis results. If applied to mucous surfaces, a severe inflammatory reaction ensues.

The meal, which is the fat-free residue of the castor bean, has poisoned cattle when mixed with fodder. The use of the meal as a fertilizer has not been without danger to man and beast. Exposure to its dust has caused irritation of the nasal and conjunctival mucous membranes. It is obvious, therefore, that the careless handling, in the industries, of the castor beans and of the castor meal is fraught with grave consequences. Kobert[2] lists the following signs and symptoms of ricin poisoning in man: Nausea, vomiting, stomachache, colicky pains, diarrhea, at times bloody evacuations, tenesmus, headache, fever, hot skin, burning sensation in the throat, thirst, clammy perspiration, small and rapid pulse, cramps in the legs, dilatation of pupils, cyanosis, and anuria.

The case, herein recorded, presents features which have not been mentioned in the literature. The symptom-complex warrants the diagnosis of protein sensitization, occupational in origin, due to the castor bean. The subject is that of a white male, aged twenty-seven, a chemist by occupation and engaged in the "Drug, Poisonous, and Oil Plant Investigations of the Bureau of Plant Industry of the U. S. Department of Agriculture." He has always enjoyed good health and has had no operation performed on the nose or throat. Employment in the Bureau dates back to 1913. Prior to 1916, there had been no sensitiveness to dust of any kind. In 1916, after three years of service, the subject noticed that

exposure to dust was accompanied by itching of the eyes, lachrymation, sweating of the forehead, sneezing, and coryza. The sneezing would be continuous for fifteen to twenty minutes. The administration of atropine and the use of adrenalin-spray did not control the symptoms. The attacks of sneezing were more frequent and severe in the spring, April to May, and in the fall, the latter part of August and September. There was no family nor personal history of asthma or of hay fever. During the eighteen month period from December, 1917, to July, 1919, the subject was free of symptoms. In this interval, he was in the military service and was assigned to a serological laboratory. After his discharge from the army, there was a return of symptoms with the resumption of his former duties in the Bureau of Plant Industry. The symptoms were, however, aggravated by attacks of asthma during the night. Severe sneezing spells during the day inevitably ushered in attacks of asthma during the night. Frequently he was aroused out of a sound sleep by asthmatic attacks.

In November, 1921, the subject was afflicted with the usual attacks of sneezing while working with the short ragweed. During the night, the attack of asthma was of exceptional severity so that he felt as if "he were going to die." He was incapacitated from work for the two following days.

In virtue of the history of perennial hay fever, more prominent in the spring and in the fall, cutaneous tests were performed (November 15, 1921) with the hope of discovering the sensitizing agent. The materials employed were as follows:

Right forearm: Control decinormal NaOH solution, pollen-extract of red top, timothy, June grass, cocklebur, ragweed (short), cosmos, ash, dandelion, dock, sweet vernal, willow and black walnut.

Left forearm: Alcoholic saline extract of the pollen of ragweed (short) A, chenopodium album, ragweed (short) B, sodium hydrate extract of the pollen of ragweed (short), pollen of chenopodium ambrosioides and pollen of ragweed (short).

The cutaneous tests proved negative with all the above-mentioned pollens and pollen extracts.

The second series of cutaneous tests was prompted by the suspicion of the subject that the dust of the castor bean was the specific exciting cause. He recalled that, in 1916, investigations of the castor oil were undertaken in the Bureau and the extraction of the oil from the beans formed a new part of the routine of the laboratory. Coincident with this investigation, symptoms of irritation of the nasal mucosa appeared. There was a constant exposure to the dust of the fat-free meal. This, when dry, consisted of a fine, dirty-white, amorphous powder. The slightest inhalation of the powder while at work brought on attacks of sneezing.

The pouring of the meal into bags by an associate in one end of the laboratory inevitably produced sneezing in the subject, while engaged in reading or writing at his desk at the other end of the laboratory. Even the necessary moving about of the sacks of castor beans by charwomen in the early morning hours caused sneezing of the subject upon first entering the room. Invariably emptying the sacks or stumbling into them, with or without the knowledge of the subject, gave rise to symptoms. The severity of the attacks of sneezing was determined by the amount of dust afloat.

Accordingly on November 18, 1921, cutaneous tests were performed with the castor meal. Decinormal sodium hydrate solution was employed as a solvent. Other materials were added for control observation.

The details of the second series of skin tests follow: Five drops of decinormal sodium hydrate solution were placed one-half inch apart on the anterior aspect of the left forearm. A slight superficial scratch was made through each drop with a fine needle. The first drop just below the end of the elbow served as a control. The test materials were then applied in the following order to each drop of alkali by means of the flattened end of a tooth pick: Control of sodium hydrate solution, castor meal powder, pollen of ragweed (short), horse serum protein, and castor meal powder. Within fifteen minutes, wheals developed at the site of drops, numbers 2 and 5, to which the castor meal had been applied. The wheals were irregular in outline, showing numerous pseudopods, the upper one measuring 17 mm. and the lower one 10 mm. in greatest diameter. At the end of the half-hour, the entire forearm was one erythematous patch. The lymphatic trunks on the inner aspect of the upper arm appeared as reddish streaks. Moreover, wheals were formed approximately 7 mm. in diameter at the site of the other drops.

It is to be emphasized that every precaution had been taken to prevent the inhalation of the fine particles of organic matter during the transfer from bottle to the arm. Obviously, dust formation was impossible when once the test material became moistened with the sodium hydrate solution. The development of a constitutional reaction at the end of fifteen minutes was, indeed, a surprise. The conjunctivæ became engorged. Lachrymation and coryza were profuse. An attack of sneezing added to the discomfort. The subject felt nauseated and experienced a sensation of weakness in the abdomen. There was, also, moderate flushing of the face and perspiration of the forehead. Full recovery was made within half-hour of the onset of the reaction. Absorption, therefore, of the minutest amount of castor meal solution from two superficial abrasions on the forearm reproduced the clinical symptoms ordinarily occasioned by the exposure to large doses of the dust of the castor meal.

Thirty-five minutes after the above test had been begun on the left arm, the following materials were employed in similar manner on the anterior aspect of the right forearm: Control of sodium hydrate solution, pollen of ragweed (short), horse serum protein and chicken feather protein. These tests proved negative. It will be recalled that the sodium hydrate solution, the ragweed pollen, and the horse serum protein each gave a delayed reaction with the formation of a 7 mm. wheal on the left arm. Undoubtedly, the delayed reaction was an expression of the increased circulation of lymph in response to a powerful local irritant. The negative cutaneous reaction of the same materials on the other arm indicated a lack of sensitiveness on the part of the subject to them.

It became a matter of interest to determine quantitatively the degree of sensitiveness to the castor meal. Accordingly, 1 gm. of the fat-free meal was treated with 100 cc of a 12 per cent alcoholic saline solution. The mixture was shaken for forty-eight hours, centrifuged, and the supernatent fluid was pipetted off. The fluid, representing the stock solution of 1:100, was clear and colorless. Dilutions were made from the stock as high as 1:1,000,000. Cutaneous testing with the varying dilutions of the soluble proteins was completed in two trials on December 15, and 18, 1921.

A definite wheal, 3 mm. in diameter, was produced by a drop of the protein extract in the dilution of 1:250,000. No reaction was obtained with the higher dilutions. The wheals, produced by the lower dilutions, gradually increased in size; the stock solution formed a wheal 17 mm. in diameter which made its appearance in five minutes. No constitutional effects were noted on these two occasions.

The attempt was next made to establish which protein constituent of the fat-free meal might be the sensitizing agent.

Four preparations were used, which were obtained in the following manner: The fat-free castor meal was extracted with a 10 per cent sodium choloride solution. The mixture was filtered. The filtrate, designated A, was a deeply straw-colored fluid. The residue, designated B, was a mealy powder. Solution A was then boiled and filtered. The filtrate, C, was a light straw-colored fluid, and the residue, D, after washing and drying, consisted of a light brownish crystalline powder.

On February 3, 1922, the above mentioned test materials, A, B, C, and D, were applied to the anterior surface of the left forearm. The smallest possible drops of liquids, A and C, which would adhere to the under surface of the corks, were deposited on the skin and a superficial scratch through the epithelial layers was made with a fine needle. Powders B and D were each mixed on the skin with a drop of decinormal sodium hydrate solution and the usual skin scratch was made. The amount of the powders used was such as could be gathered on the flattened tip of a toothpick.

Two minutes after the application of the test materials, the subject experienced itching at scratch marks A and C, which were bathed with the liquid reagents. Soon wheals appeared at A and C, and at B and D. Five minutes later, constitutional effects were in evidence. The subject complained of itching at both wrists and in both palms. He seemed restless. The palms began to sweat. This was followed by itching and perspiration of the forehead. Within fifteen minutes, the constitutional effects were most marked. The subject sneezed eight times in succession; he complained of nausea and then vomited four times. The conjunctivæ were injected. The face was flushed. The temporal arteries became prominent. The pulse was full and bounding. The subject stated that his heart thumped violently. The general reaction was so acute that it necessitated the subcutaneous administration of 1 cc of adrenalin solution. This happily brought relief.

The cutaneous reactions were read at the end of twenty minutes. The wheals produced at A measured 15 mm., at B 10 mm., at C 12 mm., and at D 15 mm. Solutions A and C, as previously mentioned, were the first to produce a local response and the induration about these two scratch marks persisted over night.

It would seem as if the protein constituent chiefly concerned in causing the local reaction were soluble in 10 per cent sodium choloride solution and non-coagulable—a globulin in character; and that the reactions obtained with powders B and D were secondary to the intense local irritation. This cannot be stated with certainty. Cutaneous testing with each protein fraction at different times might have cleared up this point. The subject, however, was averse to further tests.

It is of interest to note that, despite the presence of the toxalbumin in the castor meal, cutaneous tests in other individuals have proven negative. Eleven asthmatic and six hay fever patients have been tested with the same specimen of meal, and the cutaneous tests have in all instances been negative.

Furthermore, five other associates of the subject have been engaged in castor bean investigations in the laboratory. They have been exposed to the organic dust even more intimately than our subject. This was particularly true during the war when the exigency demanded intensive study. Only one of the five workers showed a slight tendency to sneezing while engaged in the work. This tendency was only transitory. During this period, the subject was in the military service and did not suffer from the specific symptoms.

The danger to workmen resulting from exposure to the castor bean in the industries has been emphasized by Kobert. Curiously enough, no mention has been made by him of any symptoms comparable with those of the case described. Kobert[3] has prepared a "Ricinusheilserum" for rendering workmen, who handle

the pressed cake, immune to the poisonous constituent. The use of the "Ricinusheilserum" in relieving inflammation of the eyes is recommended.

In this connection, the following statements from two of the largest castor-oil manufacturers in this country are noteworthy:

"We know by experience that the dust from the whole castor beans and also from the castor pomace, after most of the oil is extracted, is effective on people that are subject to asthma. People that work in our factory are troubled more of less until they get what you might call acclimated." The second statement reads: ". . . up to the present time we have never noted anything of this kind among our employees. However, in the handling of castor beans in our plant there would be only one man that would be likely to come in contact with this dust, as the beans are all received in bags and the bags are opened and emptied into a trap-door receiver. After that they are handled by machine conveyers until they reach the presses, so that the only man that would come in contact with this dust would be the man who cuts the bags at the time they are emptied; as this is done in a large open space, and the bag being cut at the place of emptying, this man would not be likely to be affected by the dust."

Sensitization to organic dust in occupation has been recognized as a cause of asthma and of perennial hay fever. Its mechanism, however, is not fully understood. Thorough investigation of the occupational history of patients assumes great importance. Cutaneous tests with the suspected materials not only determine the diagnosis, but also expedite treatment. They may in some cases indicate the advisability of change of occupation. Thus Walker[4] records the case of a jewel polisher who became sensitized to boxwood dust. Several inoculations with boxwood protein enabled the patient to continue at his work, freed from symptoms of perennial hay fever. Peshkin[5] cites a case of a pharmacist who developed bronchial asthma because of an acquired sensitiveness to the powder of ipecac. Relief from asthma followed a change in occupation. In the experience of Rackemann,[6] a coffee worker with a positive skin reaction to coffee dust and eight professional bakers with positive skin reactions to wheat proteins are included.

In our subject, desensitization with a protein extract of the fat-free meal was considered. The inherent poisonous qualities of the substance, however, discouraged the attempt, despite the successes of Ehrlich.[7] The latter established an immunity in white mice toward the toxic effects of ricin by feeding and by subcutaneous injections of preparations of the toxin. On March 3, our subject was transferred to another laboratory at his request. To date he has enjoyed entire freedom from attacks of sneezing or of asthma.

Summary and Conclusions.—1. A chemist acquires in course of his occupation a sensitiveness to the dust of the castor bean.

Attacks of sneezing and of asthma are the clinical manifestations of this sensitiveness.

2. The fat-free castor meal produces an urticarial wheal at the site of a superficial scratch on the forearm.

3. A cutaneous reaction is obtained with a drop of the protein solution of the meal in a dilution of 1:250,000.

4. Symptoms of protein intoxication result from the absorption of extracts of the castor meal from skin abrasions.

5. The presumptive evidence indicates that the globulin fraction possesses antigenic properties.

6. Exposure to organic dust in industries may cause an acquired sensitiveness. Cutaneous testing with the suspected material is of value in diagnosis and treatment.*

* It is a pleasure to record my thanks to Dr. W. W. Stockberger, Physiologist in Charge of Drug, Poisonous and Oil Plant Investigations of the Bureau of Plant Industry of the U. S. Department of Agriculture, and to the members of his staff for many courtesies.

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THE DIAGNOSIS OF OBSCURE CHRONIC ABDOMINAL CONDITIONS.*

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The diagnosis of chronic abdominal disorders is, as a rule, far more difficult than the diagnosis of acute lesions of the same variety. The very nature of the acute case with its more or less stormy onset has, as a rule, something characteristic of its causation. All the exact methods of the last decade have not made the diagnosis of the chronic abdomen a sinecure. Even the roentgen ray, so widely heralded that most of our patients request its use before submitting to an operation, not infrequently leads us into error.

The typical chronic cases are usually easy to recognize. It is

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the obscure case of one kind or another which intrigues and puzzles the most expert diagnostician. The obscure cases under consideration are the more common intra-abdominal conditions with atypical symptoms, leaving out of consideration the surgical rarities which we occasionally encounter. Fortunately, particularly in large clinics, the so-called exploratory laparotomy is fast finding its way into the discard. The well-regulated hospital requires a preoperative diagnosis written on the operative record, and this to be written before the completion of the operation. We are fast graduating from the custom of seeing a patient from the country at five o'clock one afternoon (still, of course, speaking of the chronic cases) and operating on him the next morning, so as to save the visiting doctor an extra trip to town.

An exact diagnosis, permitting an ordinary incision instead of a tremendous exploratory opening and a minimum of handling, ensures a rapid recovery, and not only a low mortality rate but an equally low morbidity rate. I am confident that the mortality of the so-called exploratory laparotomy is appallingly large.

There is a German medical proverb which reads, "The most common is usually there:" The most common is, of course, the appendix, and numberless cases of obscure abdominal symptoms are due to chronic appendicitis.

In the early days of gastroenterostomy, before more accurate methods of diagnosis, particularly the exact interpretation of the roentgen rays, came into general use, gastroenterostomy was frequently done without a demonstrable lesion of the stomach, trusting that a drainage of the stomach would heal the ulcer, which frequently was not even present. It is only after the lapse of years that we have been brought to realize how disastrous and harmful this operation is in the absence of a demonstrable gastric or duodenal lesion. Occasionally we still see the results of these unnecessary gastroenterostomies, where a gastroenterostomy has been done and the true cause of the abdominal symptoms, either the inflamed appendix or the chronic gall-bladder, has been allowed to remain, the patients being only the worse for their operative interference. The obverse of this picture I shall discuss later, that is, the frequent removal of the appendix when a gastric or duodenal ulcer or some pelvic disease is at fault.

The more chronic abdominal cases which come under observation the fewer true gastric or duodenal ulcers are seen. The greater the number of clinical gastric ulcers studied the more are found to be due to extragastric intra-abdominal lesions. To quote from Smitties: "The close simulation of the symptomatology of uncomplicated gastric ulcer by disease of other abdominal organs would appear to suggest that the clinical manifestations associated with ulcers are often the evidence of abdominal or other constitutional derangement, in the course of which ulcer is only an incident or an

end-result. It is within the experience of all who have had reliable training that laparotomy often fails to disclose gastric ulceration in patients presenting all the so-called characteristic symptoms of ulcerations."

It is these cases, which Moynihan has grouped under the name of "appendix dyspepsia," which form a group of particular interest. As a rule they present no history of definite attacks or inception of the disease. There is a gradual letting down of the entire organism—a loss of the feeling of well-being. There is more or less abdominal distress and pain which, as a rule, comes on after the taking of food. This distress or pain rarely approaches in severity that due to gastric or duodenal ulcer, and there is not the definite relation of pain to the taking of food. For instance, instead of the relief from pain which in gastric ulcers follows the taking of food there is, as a rule, an accentuation of pain following the ingestion of food. Unlike gastric and duodenal ulcer this pain has not the regular time for occurrence. The situation of the pain is very like that of gastric and duodenal ulcer, that is, around the epigastrium or just above the umbilicus. The pain is, as a rule, increased by exercise, which is a very characteristic symptom. Vomiting is frequent, usually at irregular intervals, and often without relation to the intake of food. Flatulence, belching and heartburn are the most distressing and constant symptoms.

In a few cases vomiting of blood is present, and in these it is almost impossible to make a differential diagnosis from clinical gastric ulcer. Why or wherefore this vomiting of blood occurs is difficult to determine. In all probability it is due to the presence of very minute toxic ulcers or erosions in the stomach which are too superficial to be discovered by roentgen ray and too small to make themselves evident by the palpation of the stomach during operation. It is in these cases that the inexperienced surgeon is tempted to do a pyloric exclusion and gastroenterostomy without the true evidence of gastric ulceration, when the removal of a diseased gallbladder or appendix will solve the entire situation.

Case I.—J. L., aged twenty-nine years, has had for five years some pain in the abdomen, often incapacitating him for work. Pain has followed taking of food, but he occasionally has hunger pains and pronounced loss of weight. Frequent vomiting, the vomiting occurring irrespective of taking food. At times he has vomited large amounts of blood. There is tenderness in the epigastrium and marked tenderness over the appendix region, with some rigidity. Wassermann negative. Occult blood in stool. Roentgen ray shows slight irregularity in the duodenum and an adherent appendix, its tip pointed upward.

Diagnosis. Duodenal ulcer and chronic appendicitis.

Operation, May 20, 1920. Gas-oxygen anesthesia, upper right

rectus incision, the appendix was found chronically inflamed, its tip adherent to the omentum, which was in turn adherent to the anterior surface of the duodenum. The adhesions were separated and the appendix removed. The duodenum where the omentum was adherent showed no ulceration. The peritoneal abrasion in the duodenum was repaired with a fine silk suture and the wound closed. Recovery uneventful and there has been no recurrence of the symptoms.

The abdominal tenderness in appendicular dyspepsia is, as a rule, of great interest. There is usually marked tenderness in the epigastrium, though rarely the same exquisite tenderness of the gastric or duodenal ulcer. A very characteristic sign is that pressure over the appendix region, frequently causing pain in the epigastrium, the same pain of which the patient is suggestively aware. If a careful and gentle examination is made in many instances there is a superficial rigidity of the right rectus, even in the absence of localized pain, tenderness on pressure or deep rigidity of the abdominal muscles. I have found this superficial abdominal rigidity a very important diagnostic sign in the differentiation of intra-abdominal conditions. In making this examination the pressure must not be sufficient to cause any pain sensation. Only the lightest and most gentle touch must be used. In many instances it has proved of greater value than the tenderness or deep rigidity.

The symptoms of appendix dyspepsia are so variable and, as a rule, so atypical that only by repeated examination and frequent taking of the history can a diagnosis be arrived at.

The question how morbid changes in the gall-bladder and appendix induce symptoms in other viscera and distant parts has been ably discussed by Rolleston, who divides the causes into reflex, mechanical, toxic and infectious.

"*Reflex.* Irritation in the appendix or gall-bladder may cause hypertonus of the stomach and spasm of or failure to relax on the part of the pyloric or ileocecal sphincter, leading to gastric or ileal stasis and so to excess of acid or to toxemia. . . . Hurst has seen visible spasm of the middle of the stomach when the appendix is manipulated under the roentgen ray. . . . In the case of chronic appendicitis failure of relaxation of the ileocecal sphincter is thought by Hurst to be commoner than spasm. Cecal stasis from inhibition of peristalsis or from enterospasm (spastic constipation) may be due to chronic appendicitis. Appendicitis may reflexly lead to increased frequency or inhibition of micturition through an irritated focus in the spinal cord (Mackenzie), and chronic irritation of the appendix may be responsible for cardiac irregularities.

The reflex pain in the epigastrium, which is so common in the appendix and gall-bladder dyspepsia, has given rise to some discussion. Mackenzie maintains that it is in the peripheral termination

of the sixth and seventh dorsal nerves in the abdominal wall, and that this depends on the irritated focus in the spinal cord, whereas Hurst argues that the pain is visceral, in the pyloric end of the stomach and due to the hyperperistalsis. They both, however, agree that the epigastric tenderness is due not to pressure on the stomach but to the irritated focus in the spinal cord, which causes an exaggerated sensory effect when the skin, and especially the muscles and the underlying subperitoneal tissues, are pressed on. Very often the appendix when removed shows little naked-eye change to correspond with the prominent symptoms that then disappear. Microscopic examination may be necessary to reveal the evidence of past inflammation in its walls, especially fibrosis in the submucous coat, and often, as I have seen in many sections, the changes are very slight.

Mechanical. Pericholecystic adhesions may embarrass the movement of the stomach, interfere with the passage of food through the pylorus or even lead to the hour-glass stomach. . . . Pericecal adhesions may cause intestinal stasis and so toxemia, and the same result, only in a more marked degree, may be produced by an appendix adherent across the lower part of the ileum.

The appendix adherent in the pelvis explains a very interesting and apparent paradox in the symptomatology of chronic appendicitis. Most cases are more comfortable and have less frequency of pain when the bowels have moved well. This is a most common feature of chronic ileocecal appendicitis or retrocecal appendicitis. There are, however, occasional cases in which the pain is less when the bowels are constipated. In this class of cases the cause is as follows: the appendix is adherent by the tip in the pelvis; the loaded cecum releases the adherent appendix and relieves the pain. On taking a laxative and emptying the cecum the latter tends to draw high up in the abdomen and so increase the pain.

The toxic and infectious origin of gastric symptoms in diseases of the appendix and gall-bladder are more easily understood and depend upon the absorption of septic contents, the same as in any other source or focus of infection.

As Munsell has said, "It is a group of symptoms and perhaps signs which point so strongly to organic gastric or duodenal disease that it is only by the most careful examination or by the fortunate supervention of definite appendicular symptoms that a correct diagnosis is possible."

A typical case of this kind is as follows: CASE II.—A doctor in a neighboring city has complained of pain in the abdomen for eleven years. This pain centered in the umbilicus and was of an irregular nature. There was an increase of the pain after taking food and an accentuation after exercise. During this eleven years the pain has intermitted for several months at a time and was usually restarted by an overindulgence in food or an indulgence in alcohol. He was treated

for nervous indigestion for many years, and finally sought the advice of one of the most prominent stomach men in the country. A very careful examination was made, including roentgen-ray and fractional gastric analysis. The gastric analysis showed increase in the free and combined acids. As far as could be learned the roentgen-ray picture showed what was thought to be a gastric ulcer on the lesser curvature. He was put on the Sippy treatment and temporarily improved, and was advised if the pain recurred to submit to an operation.

In February, 1921, the pain was of unusual severity, started at the umbilicus and radiated toward McBurney's point. I saw him at this exceedingly opportune time, during an exacerbation of the symptoms. His temperature was normal, his pulse slightly accelerated and there was marked tenderness and rigidity over the epigastrium. There was vomiting which contained no blood and a marked rigidity and tenderness over McBurney's point. On pressure over McBurney's point the tenderness was referred to the epigastrium. I advised him to come to the city, where further examination was made. Gastric analysis showed hyperacidity. Roentgen-rays revealed gastric hypermotility without evidence of gastric or duodenal disease, and a long irregularly filled appendix with its tip pointed toward the pylorus. Fluoroscopically the cecum was immobile and tender to pressure.

A diagnosis of appendicitis was made and an operation done. A very long appendix, about nine inches in length, was removed with a stricture and adhesions about the middle and the tip pointing toward the pylorus. Postoperative recovery was uneventful and the patient has been completely relieved of his symptoms.

This is characteristic of a group of cases in which the occurrence of acute supervening symptoms point definitely to the diagnosis. The sufferers from chronic appendicular dyspepsia lead the lives of invalids and have travelled the rounds from doctor to doctor with the usual diagnosis of chronic nervous indigestion.

The comprehensive diagnosis and treatment of these cases is made much more difficult by the frequency of associated true disease of the appendix, gall-bladder and stomach. It is probable that the association of these diseases is not only clinical but more probably pathologic. According to Deaver's view, in which I concur, the appendix, which is so frequently affected alone, so far as pathologic and clinical evidence is concerned, is usually the first offender, involving the other organs by sepsis, toxins or reflex nervous phenomena. In many instances the timely removal of the diseased appendix may prevent the formation of gastric or duodenal ulcer. The roentgen-ray examination, so valued in the diagnosis of lesions of the stomach and duodenum, frequently leaves us in the lurch in the diagnosis of chronic appendicular conditions, and is right about as often as it is wrong. If the appendix is not seen at all

it is interpreted as being constricted so that the barium meal cannot enter, or it is said to be retrocecal, and according to the views of many observers, nearly all retrocecal appendices are pathologic, and conversely an irregular filling defect may be interpreted as being irregular fibrous bands constructing the appendicular lumen.

What is important in these cases is the tenderness of the filled cecum under the fluoroscope and the absence of cecal and appendicular motility. That is, the seemingly fixed immobile cecum is apt to be the seat of pericecal adhesions due to infection of the appendix. A fixed shape and anchorage of the appendix seen on several plates at different times is strongly suggestive of appendicular change, as the normal appendix changes its form and position during the digestion of food, moving with the cecum.

There are some cases of appendicular or gall-bladder dyspepsia simulating gastric ulcer in which, due to the reflex pyloric spasm, there may even be a simulated roentgen-ray picture of gastric or duodenal ulcer. When there is the slightest doubt it is wise to have the roentgen-ray examination repeated after a two-day or three-day interval. A gastric or duodenal lesion once shown on the roentgen-ray plate or once visualized on the fluoroscope can be shown again if it is present. If, on the other hand, the second or third roentgen-ray place fails to disclose the lesion it is certainly not there. A case of this kind is rather interesting:

CASE III.—Male, aged thirty-six years. Six months before I saw him he began to have severe pains in the epigastrium accompanied by vomiting. The pain came on with increased severity after taking food and was increased by exercise, so that the man was unfitted for work. There was no vomiting of blood. Gastric analysis showed slight hyperacidity. There was slight tenderness just to the right of the umbilicus and over the appendix region; no occult blood in the stool. Wassermann negative. Roentgen-ray examination, October 15, disclosed a filling defect in the lesser curvature of the pylorus, with pyloric spasm and an irregularly filled appendix. Roentgen-ray diagnosis: appendicitis and gastric ulcer. We were not satisfied that the case was truly one of gastric ulcer, so three days later a second roentgen ray of the stomach was made, and although the spasm was present the filling defect could not be shown. Also at this time, under the fluoroscope, pressure over the cecum caused epigastric pain with an increased gastric peristalsis. Clinical diagnosis: Chronic appendicitis. Operation, October, 1921, gas-oxygen anesthesia, right pararectal incision, inspection of the pylorus, gall-bladder and duodenum revealed no abnormality. The appendix was adherent and buried in the wall of the cecum, ileocecal in position; removed in the usual way. Operative recovery uneventful. In the two months since operation the patient has regained his normal weight and is free from all symptoms.

That too much reliance must not be placed on a single series of roentgen-ray examinations is also shown by the following case:

CASE IV.—Mrs. T., aged fifty years, referred from a neighboring city with a diagnosis of cancer of the stomach. She had always been in good health until six months before, when she began to have pains in the abdomen, loss of weight and vomiting. She brought roentgen-ray plates with her, which evidently showed a pyloric obstruction. Examination disclosed a rather thin, fairly well-nourished woman. In the right side of the abdomen was a tender mass, the size of a fist, which could be moved from the epigastrium to the right iliac fossa. We thought we had to deal with a movable kidney. Roentgen-ray examination showed hyperperistalsis of the stomach. Under the fluoroscope the mass was seen to be a cecum mobile. The irregularly filled appendix was seen retrocecal. The kidneys were in their normal place. Diagnosis: cecum mobile and chronic appendicitis. Operation, November, 1921, gas-oxygen anesthesia, right pararectal incision. The cecum was found freely movable with the appendix adherent to its posterior surface. The appendix was removed and the cecum anchored. Postoperative recovery was uneventful and she has been free of her symptoms ever since.

The reason for the misreading of the first series of plates was probably the position in which they were taken, that was flat on the back instead of in the upright position, so that the contour of the barium meal was due to the pressure of the loaded stomach on the spinal column.

After appendicitis the most frequent cause of ulcer symptoms without the presence of an ulcer is gall-bladder inflammation with or without stone.

For one who looks only for the classic signs of gall-bladder disease—pain, colic and jaundice—many cases will entirely escape detection and will be consigned to that unknown land of chronic dyspepsia and nervous indigestion. Long-continued gastric indigestion in a woman past forty years is always more or less suggestive of gall-bladder disease, although the more we see of gall-bladder disease the less important is the age factor and the more cases we see in young individuals. The constant indigestion, gas eruptions, vomiting at irregular intervals and constant epigastric distress are always suspicious. This epigastric distress may never reach the point of pain, but is, as frequently, more a fulness or sense of weight.

There are a few cases, and one in particular has come to my notice, in which the only single symptom was backache located between the shoulder-blades. There was absolutely no indigestion and no vomiting. The only symptom she had to suggest gall-bladder disease was a slight rigidity of the right side of the epigastrium with an interference with deep inspiration on pressure. In this case the roentgen ray helped us by showing eight very small stones. Cholecystectomy was done and the recovery was uninterrupted, with a complete disappearance of the symptoms.

Gastric analysis is little help, as either a hyperacidity or a subacidity may be present. A very positive sign is the interference

with deep inspiration when pressure is made over the gall-bladder region. With the patient flat on his back, his knees flexed, firm pressure is made under the right costal arch and the patient is requested to take a deep breath. In the presence of gall-bladder inflammation, even of a minor degree, the breath is stopped with a sharp catch, short of full inspiration. If this is present on the right side and absent on the left this sign almost invariably points to gall-bladder or liver inflammation. I have never found the so-called tender points in the region of the scapula or spine of much assistance.

The roentgen ray in these cases as frequently leaves us in the lurch as otherwise, and for the benefit of our diagnostic acumen it is perhaps just as well, as we are forced occasionally to make a diagnosis on our unassisted powers of observation.

A rather interesting and not common extragastric lesion which may closely simulate gastric ulcer is epigastric hernia, the rarity of which is evidenced by Coley's statistics; among 3383 cases of hernia only 3 were of the epigastric variety. The large ones are very easy to recognize. Occasionally, however, they are only of minute size, and only the most careful palpation of the linea alba above the umbilicus may disclose their existence, and then only if the examiner is on the lookout. These cases frequently have excruciating pain, closely simulating that of gastric ulcer. The pain may be of such severity as to interfere with the patient's activity. There may also be periodic attacks of vomiting, absolutely independent of the intake of food. They rarely, however, show the emaciation and evidences of chronic invalidism following gastric or intra-abdominal disease. The lesion begins as a small protrusion of subperitoneal fat through a transverse slit in the linea alba. In very early cases there is frequently no true sac but simply a protrusion of subperitoneal fat. Moschcowitz reports two cases in which there was not even a protrusion of subperitoneal fat. There was in these cases merely a small slit in the viscera through which protruded a single large vessel. The vessel was tied off and the slit closed and the pain in both cases was relieved. The second degree contains a true empty small sac and a third a small piece of usually adherent omentum. They are rarely of sufficient size to contain intestine, though Gatewood has reported a case in which there was an intestinal strangulation. It is, however, only the small epigastric hernias which particularly interest us, because of the difficulty of diagnosis and because of the symptoms they present out of all proportion to their size. The cause of the symptoms is probably the drag on the parietal peritoneum, and a very frequent sign is the increase of pain after exercise. We have had several cases of this kind in all of which the recovery was complete after operation.

Lewisohn, in speaking of these cases, sounds a timely warning,

which is not to be certain, in the presence of epigastric hernia, that the symptoms are entirely due to the hernia. In his service at Mt. Sinai Hospital he has seen several cases in which the symptoms persisted after an operation for epigastric hernia and in which further investigation and subsequent operation disclosed intra-abdominal lesions.

We have been speaking thus far of symptoms of gastric and duodenal ulcer which are due to less serious intra-abdominal lesions. The reverse side of the picture is equally obvious and neither so simple nor so pleasant. That is the numberless cases in which an appendix or gall-bladder operation has been done without relief when the trouble is elsewhere, as a rule, either a pyloric or duodenal ulcer. I venture to say that all of us have more than once made this mistake and have still more frequently done so without having had the opportunity of knowing it—this because of the frailty of human nature, and patients are prone to seek elsewhere when an unsuccessful operation has left them unbenefited. It is only by the most painstaking care and the weighing of every scintilla of diagnostic evidence that we can avoid making these diagnostic errors, and when our diagnostic means fail then and then only should we make a so-called exploratory laparotomy.

One of the most important factors in the diagnosis of all chronic cases, abdominal or otherwise, is the search for syphilis. This has been particularly brought to my attention by the occurrence of several distressing experiences. There is no symptom-complex of any intra-abdominal disease which cannot be simulated by syphilis. In a recent communication Salzer has reviewed the records of 150 consecutive private patients who presented themselves for examination for chronic conditions. As a matter of routine a Wassermann was taken in every one of these individuals. These cases were in no wise venereal cases but represented the ordinary run of cases which seek the assistance of the internist for chronic conditions. Of these 150 cases 24 showed a positive Wassermann, and of these 24 cases only 5 gave a definite history of syphilitic infection. Of these 24 cases 6 had undergone abdominal operations, from which they had been absolutely unrelieved of their symptoms. Of these 6 all had had appendix operations in addition to one kidney operation, two ovarian operations and 1 in which three distinct operations had been done for abdominal adhesions, besides numerous sacrifices of teeth and tonsils. It is only of late years that we have come to appreciate the protean aspects of congenital syphilis. The opportunity of examining a large number of men in the army undoubtedly threw a great light on this subject. What is important to bear in mind is that congenital syphilis may exist without any of the so-called stigmata for which we have been taught to seek, and undoubtedly many of these cases with obscure abdominal symptoms are of congenital origin.

Several experiences of my own have led me to the taking of

Wassermanns in all chronic abdominal conditions. Three of these cases are of particular interest.

CASE V.—Female, aged thirty-two years, has been troubled for years with frequent gastric disturbances—pain after eating, flatulence, tenderness in the epigastrium and hyperacidity. Roentgen-ray examination was entirely negative except for a slight increase in tenderness over the cecum and the fact that the appendix could not be shown. She was seen in consultation with a reliable internist who made the diagnosis of appendicular dyspepsia and advised operation. Through a long pararectal incision, under gas-oxygen anesthesia, the entire abdomen was explored and nothing abnormal was found except a slightly inflamed retrocecal appendix, of normal size, without adhesions. The appendix was removed in the usual way and the abdomen closed without drainage. Postoperative recovery was uneventful, and for some time, as is very often the case, the symptoms were entirely relieved, only to recur with increased severity. Some months later a blood examination was made and a 4-plus Wassermann was found. The history taken with this lead pointed definitely to congenital infection. Treatment improved the condition and entirely relieved her abdominal and gastric symptoms.

CASE VI.—This case represents a class of parasyphilitic diseases with a definite symptom-complex of cholecystitis. The man when first seen had been suffering for three years with obscure symptoms of indigestion, with infrequent attacks of nausea and vomiting. There was no history of definite gall-stone colic. There was, however, a marked tenderness over the gall-bladder, which was somewhat distended and interference with inspiration on deep pressure. Roentgen-ray examination was negative except of a prolapsed and dilated stomach. Constipation had been marked for several years. Gastric analysis showed nothing unusual. March 23, 1917, incision over the gall-bladder region revealed a distended gall-bladder without any adhesions. Normal pylorus and duodenum. The appendix was slightly adherent but otherwise normal. The appendix was removed and the gall-bladder drained. Postoperative recovery was uneventful. This man was not relieved of his symptoms in any way. Three years later he was seen by an internist, having passed out of my hands. A Wassermann was taken, which was found to be positive. Antisyphilitic treatment was instituted and recovery from his gastrointestinal symptoms was prompt.

That a typical picture of gastric or duodenal ulcer can be simulated by syphilis is well known. This may either be due to a true gumma of the stomach, demonstrable syphilitic lesions in extragastric organs or by producing changes in the central and sympathetic nervous systems. Eusterman has reported a series of 23 cases and Smitties a series of 21 cases, all presented on clinical,

roentgen-ray and serologic studies. The symptoms are typical of gastric or duodenal ulcer, including pain, loss of weight, vomiting and hematemesis. If a syphilitic history is obtainable a lead to a diagnosis is easily established; but even in the absence of a history a Wassermann is essential. If the Wassermann is negative and the history, nevertheless, points to syphilis a provocative salvarsan injection should be made and another Wassermann taken. These cases are, as a rule, diagnosticated and treated by the internist, and rarely fall into the hands of the surgeon. I venture to say that if the routine taking of Wassermanns were done a large number of gastric operations would be found unnecessary. The case which follows is what I consider a classic case of syphilis with symptoms of gastric ulcer:

Case VII.—W. M., aged thirty-nine years, service of Dr. Morris, Cincinnati General Hospital, admitted November 23, 1921, complain of pain in the stomach and loss of weight, the pains in the stomach having been more or less constant and relieved by the intake of food. During the last attack he vomited blood. The general history is not germane to the case, except marked tenderness in the epigastrium. No tumor mass to be felt. Wassermann 4-plus positive. Roentgen ray shows nothing abnormal except marked gastric hypermotility. Gastric analysis: free acid, 35; combined, 14; total, 49. Stool, occult blood. In view of the positive Wassermann and history of syphilis, salvarsan and mercury treatment were instituted and rapid improvement made. He was discharged in a month from the date of admission free from pain and eating house diet, apparently cured.

Now just a word on the reverse side of this syphilis question: A positive Wassermann and a positive history of syphilis do not necessarily mean that the symptoms complained of are necessarily syphilitic. This is particularly important when malignant disease, particularly of the mucous membranes, is suspected. This is all the more misleading since cancer, particularly of the mucous membrane, is not infrequently engrafted on a previous syphilitic basis. If syphilitic treatment is instituted in these cases, not only is valuable time lost, but the cancerous lesion is frequently relighted to renewed activity by the administration of salvarsan.

Conclusions. 1. Many cases of clinical gastric and duodenal ulcers are due to extragastric intra-abdominal lesions.

2. A single series of roentgen-ray plates is frequently misleading, and if there is the slightest doubt a complete reëxamination is essential.

3. In the successful treatment of chronic abdominal disease an exact diagnosis is essential, and except as a last resort, so-called exploratory operation should not be made.

4. In all cases of chronic abdominal diseases a diligent search for syphilis should be made before any operation is done.

THE DIAGNOSIS OF SPLEEN FUNCTION.

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Introduction. The functional activity of various organs in the body has received ample study both clinically and experimentally. Where the organs are accessible either by means of their physiologic effects, especially where they produce an obtainable secretion, chemical tests have been developed. In the case of the organs of internal secretion, their functions are becoming better understood and tests for these are now available. As the spleen has no external secretion and no known internal secretion the results of its actions cannot be studied directly.

Tests of the functional activity of the spleen are in a comparatively undeveloped state. There are essential difficulties which this organ presents in the study of its physiology. This is especially the case because the spleen is part of a system. It is part of the lymphatic system of the body, and its function is supplemented by the lymphatic glands, while it may compensate to a degree for their various activities or deficiencies.

In considering the functional diagnosis of the spleen, therefore, it must be kept in mind that the organ is essentially a lymphatic structure. Its function is related not alone to that, but also to the function of the blood and blood-forming organs and to the liver; its roles in immunity and infection, in the metabolism of iron and in its relation to special blood diseases, have become subjects of considerable study in recent years.

The spleen function would naturally vary in different individuals, depending upon the rapidity of a disease process in the spleen, the acuteness of the disturbance of its function and the compensatory functioning of the rest of the lymphoid and hemopoietic systems.

Structure of the Spleen. The histologic details of the spleen are important as an indication of its function. The splenic artery subdivides as it enters the hilus of the spleen into numerous branches. These carry with them a covering of the capsular connective tissue, dividing the spleen by trabeculæ. Each branch supplies a section of the spleen and the final subdivisions terminate in minute capillaries. Immediately upon emerging from the connective tissue the arterioles give off minute branches which end abruptly and are surrounded by a more or less compact mass of lymphocytic cells called the lymph follicle or Malpighian body. These seem to be held together by a fine network enmeshing them, which in its turn is connected with trabecular connective tissue and a few elastic fibers around the capillary. This region is called the white pulp of the spleen.

After the follicular capillaries are given off, the central artery, leaving the follicle, becomes narrower and enters the red pulp as an arteriole, or modified capillary, with characteristic three coats. These arterioles are called pulp arteries. They have a constant diameter of 6 to 8 μ and are characterized by distinct thickness of the wall and a layer of endothelium with long nuclei which sometimes project into the lumen, which is filled with red blood cells. This arteriole breaks into a minute brush of terminal vessels, the so-called penicilli of Ruysch. These end in the spleen sinuses or lose themselves in the reticulum of the spleen pulp. The spleen sinuses are a dense plexus of capillary spaces, each varying from 10 to 40 μ in diameter. On one side they are in contact with the arterial capillaries and on the other with the veins. The assumption is that the blood entering the pulp from the arterial side must pass through the spleen sinuses to be led off through the veins. The walls of the sinuses contain stomata which permit this transmigration.

The veins are in direct contact with the stomata of the sinuses. They possess only an endothelial coat and some fine fibrillar connective tissue. These veins pass through the trabeculæ and join to form the splenic vein at the hilus.

The capillaries of the spleen, therefore, are either in contact with the sinuses which in turn are connected with the veins or end directly in the pulp in contact with the pulp cells. Injection methods corroborate this, in that the coloring matter finds its way through the vessels and in places also through unwalled spaces.

Most authors believe that there are no intraparenchymatous lymph channels, but that these occur only under the serous coat of the capsule of the spleen.

Hemolymph Glands and Accessory Spleens. The hemolymph glands are a special type of structure closely related to the spleen. They are more frequent in the embryo and may be considered as embryonic remains. After splenectomy they increase in size, containing many large red blood cells free in the meshes of the reticulum and filling up the lymph channels between the follicles.

They occur in the sheep and only inconstantly in other animals. They are found in the human body placed in the retroperitoneal fat and in the prevertebral region of the neck.

The hemolymph glands are not related to the lymphatic vessels, but are interposed in the circulatory system. The artery entering it carries with it trabeculæ from the capsule, which it leaves finally as an independent capillary, while the trabecular system is connected with the reticulum. Here, also, there occur lymph follicles. The capillaries are of similar structure to those of the spleen with prominent endothelial nuclei and thick adventitia. The venous capillaries terminate either in the lacunar spaces (venous blood sinuses) or open free into the lymphoid tissue. The venous lacunæ are filled with red blood cells which give the color to the glands.

The blood must necessarily pass into these spaces or into the lymphoid tissue before being taken up by the veins.

The red blood cells of the hemolymph glands are detained in the lymphoid tissue and the network to undergo phagocytic absorption. Both the anatomical structure and cytologic changes indicate a close functional resemblance to the spleen. The hemolymph glands permit of better study of the destructive changes of the blood than the spleen itself. They show migration of the red blood cells into the red pulp more clearly than the spleen and in that way assist the study of the spleen function. A supernumerary spleen or hemolymph glands may enlarge and assume the pathologic function of the spleen[1].

Accessory spleens occur more frequently in south Europeans than in north Europeans because of the greater frequency of tropical diseases. They also occur after splenectomy and hemolytic jaundice. This organ is analogous to hypertrophy of the remainder of a partially extirpated spleen.

Cellular Structure of the Parenchyma of the Spleen. In the red pulp the connective-tissue fibers and the other connective-tissue elements form a thick network. In the meshes of this network lie the parenchyma of the spleen and the sinus spaces. The cellular elements of the reticulum are distinct macrophages.

Von Ebner[2] distinguishes the varieties of pulp cells according to their morphology without reference to their origin, as: (1) Small mononuclear lymphocytes; (2) mononuclear, polymorphonuclear and multinuclear leukocytes; (3) nucleated red blood cells; (4) adult red blood cells; (5) large cells inclosing red blood cells or pigment granules (phagocytes); (6) free pigment granules; (7) giant cells with polylobular nuclei (megacaryocytes) occurring only in young animals; and (8) blood platelets.

The leukocytes (2) are in the majority. The lymphocytes (1) are next and the phagocytes (5) are next.

In the embryo the spleen tissue is mainly white pulp surrounding the trabeculæ and vessels. This reduces with age, and in the adult the spleen consists mainly of red pulp. The spleen follicles resemble lymph nodes in structure with a central zone of large lymphocytes showing mitosis. The periphery of the follicle consists of small lymphocytes and areas of lymph tissue radiating into the red pulp and also large mononuclear leukocytes (pulp cells or splenocytes). The lymphocytes of the Malpighian bodies may be inactive or may assume an active role as macrophages; in the latter capacity they may absorb protoplasm, red blood cell granules or the remains of other leukocytes. They also occur in many lymph glands and in bone-marrow.

Granulated leukocytes (myeloid reaction) are frequent in the red pulp under normal conditions and to a less degree in the Malpighian bodies. Eosinophilic leukocytes are also abundant wherever

there is much red-cell destruction. These facts speak for the monophyletic theory of the origin of blood cells.

Most hematologists, however, subscribe to the heteroplastic theory of the formation of granular cells. They agree that eosinophilic polymorphonuclear leukocytes develop chiefly from undifferentiated mononuclear cells within the bone-marrow and in smaller numbers within certain special tissues of the organism, particularly lymphoid tissues. Whether this development is a direct transformation from lymphocytes or is the result of maturation from metastic bone-marrow tissue is undecided. There is no conclusive evidence in favor of the theory of direct transformation of neutrophilic polymorphonuclears into eosinophils either in the blood stream or in the general tissues.[3]

The presence of nucleated red blood cells (erythroblasts) in the bone-marrow as well as in the spleen tends to establish the latter as an erythropoietic organ. There is an increase in nucleated red blood cells in the spleen in various types of anemia and infectious diseases. This occurs together with an increase in myeloid reaction.

Red blood cells that are brought by the splenic vessels and have entered the pulp may be absorbed by erythrophages or destroyed and hemolyzed in the pulp, or may return to the circulation. The erythrophages are large pigment-containing cells in the spleen, the pigment being derived from the breaking down of red cells in the parenchyma. Megacaryocytes in the spleen occur in many animals, but only in young human beings. They seem to have a relation to blood platelets, occurring often after bleeding and in the region of the Malpighian bodies. Little is known of their relation to human pathology.

To sum up, the parenchyma of the spleen consists of a mass of cells. It is possible that the Malpighian follicles are the physiologic place of origin of the functionating cells produced in the spleen. It is asserted that the different regions of the spleen have different functions.

This is supported by the fact that exposure of rats to the roentgen-ray first destroys the cells of the follicles and the pulp elements remain unchanged until after much longer exposure. The different reaction of pulp and follicle in the leukemias also supports this theory. In myeloid leukemia the pulp shows hypertrophy, whereas in the lymphatic form the follicle shows hypertrophy.

The Fate of Injected Foreign Bodies. In the white pulp of the spleen one finds red blood cells lying among the lymphocytes. These show that the arterial capillaries open upon the spleen pulp. However, the other belief is that these cells as well as the leukocytes of the spleen pulp were formed there. Both leukocytes and red blood cells are known to pass through the wall of the capillaries by means of diapedesis.

Experimental intravenous injections of India ink, cinnabar pig-

ments and chicken red blood cells were made into dogs. Five minutes after, the dogs were killed and the foreign body was not found in the sinuses of the spleen but in the parenchyma and especially in the peripheral zone of the Malpighian body. This implies that the India ink travels by way of the follicle capillaries into the red pulp. A small lodgment of transfused chicken red blood cells was found among the many red blood cells of the parenchyma and relatively few in the sinus spaces. Most of all the foreign red blood cells occurred in the periphery of the follicles and in the meshes of the reticulum between the lymph cells. This shows that the foreign red blood cells entered the parenchyma through the open ends of the arterial capillaries. After that the cells might return by way of the spleen sinuses.[4]

Venous Stasis in the Spleen. Venous stasis in the spleen is another means of analyzing the function of its sinus spaces. After experimental ligation of the splenic veins there is a distinct exudation of red blood cells into the spleen sinuses and pulp. In an earlier stage only the sinuses fill with the red blood cells, whereas the pulp or parenchyma shows only edema. In from two to twelve hours the red blood cells absorb first from the parenchyma, whereas the congestion of the sinus spaces remains for a long time and the pigment content after such an experiment is no greater than normal.[5] It may be that the red blood cells gather in the spleen sinuses to return unchanged to the circulation.[6 7] This is contradicted however by the following experiments.

Ligation of the splenic veins in dogs gives an increase of venous pressure. Electrical stimulation of the efferent nerves of the spleen increases the venous blood-pressure still further. If the nerves are, however, cut infarction of the spleen takes place within twenty-four hours. These experiments show that red blood cells which have exuded and lodged in the parenchyma of the spleen after venous stasis find great difficulty to return into the general circulation.[8]

Another belief opposes this view of the direct transmigration of red blood cells from the sinus into the parenchyma. According to this the stasis of the sinus produces edema of the parenchyma, and the edema prevents the invasion of the parenchyma by formed elements; the stasis of the sinus also hinders the circulation in the arterial capillaries and forces the blood from the capillary toward the parenchyma.[9]

Methods Available for the Study of Spleen Function. The following methods have been utilized for the study of the various functions of the spleen:

1. Cytologic analyses of the blood.
2. Chemical analyses of the blood.
3. Resistance of the red blood cells.
4. Relation of hemoglobin to hematin and biliary pigments.
5. Relation of the spleen to iron metabolism.

6. Effects of splenectomy.
7. Effects of spleen feeding.
8. Effects of roentgen rays.
9. Clinical signs of functional disturbance of the spleen.

Cytologic Analyses of the Blood. From the cytologic analyses of the peripheral blood the condition of blood formation and blood destruction can be told only in extreme cases.

Megalocytes are considered young red blood cells prematurely emitted into the circulation, as after severe hemorrhage. Grawitz considers these cells the degenerative forms, their size being due to imbibition of water.[10]

Eppinger considers microcytes also newly formed cells, but Biernacki considers their form due to deficient blood plasma.[11]

Poikilocytes are degenerating cells; the megaloblasts, mitotic figures and erythroblasts indicate bone-marrow stimulation. Polychromatophilia indicates aging of the red blood cells. Basophilic stippling, according to Grawitz and Naegeli, is a sign of degenerative changes.[12] Others believe that the stippling is a caryolytic phenomenon and the cells are analogous to the nucleated reds, indicating an excessive production and output of red blood cells. These have the same resistance to hypotonic solution as normal cells. A granulofilamentous substance occurs in red blood cells as a postvital phenomenon.[13] High color-index occurs in pernicious anemia and usually indicates an accelerated regenerative function of the bone-marrow.

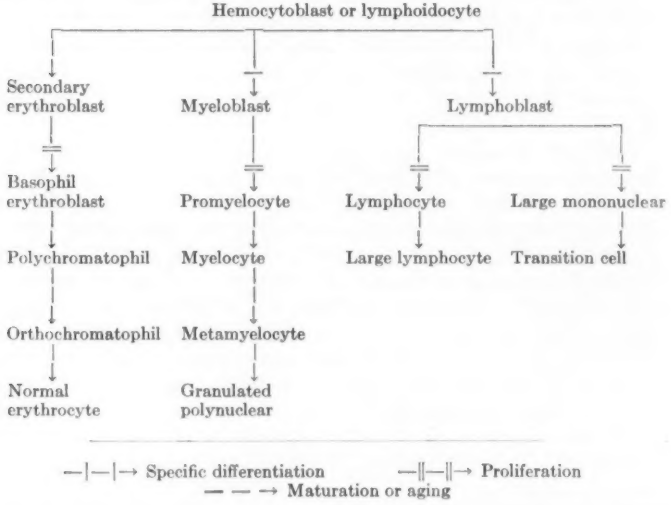
The Dualistic and Monophyletic Theories. It is generally believed that the white blood corpuscles of mammals come from two distinct sources, the lymphocytes and mononuclears from the spleen and lymphatic glands and the granular leukocytes from the bone-marrow. Ehrlich was probably the first to bring into prominence this dualistic theory.[13]

French writers particularly, on the other hand, support the monophyletic theory of the genealogy of blood cells from a single type.[14] Rieux describes three phases of cellular development:[15]

1. A process of specific differentiation. This is fundamental. The primary embryonal mesenchymatous cells out of which the blood is developed are totally undifferentiated. By differentiation the mother cell gives rise to three main forms of blood cells:
   (*a*) Erythroblast, which is the head of the hemoglobin series.
   (*b*) Myeloblast or leukoblast, which heads the myeloid series.
   (*c*) Lymphoblast, which gives rise to the lymphoid series.
2. A process of proliferation and multiplication by karyokinesis.
3. A process of maturation and of aging by ontogenesis, which is common to all blood cells and is the natural consequence of their fundamental quality as they are mobile and migratory cells.

The nucleus and the protoplasm both partake of these processes. As the nucleus is spherical in the young cells, with a tendency toward

polymorphism as it grows older, it may show pyknotic degeneration and expulsion as in the red blood cells. The protoplasm which is very fine in the young cells becomes coarser and takes on acid-staining properties as it grows older. These facts can conveniently be schematized in the following genealogical tree:



Thus, then, the differentiation of these primary cells once established and their proliferation observed the daughter cells present cytologic characteristics, fixed and specific, by which we can tell the type and age of the blood cells.

The two theories of the significance of mononuclear leukocytes are: (1) That they are an earlier stage of granular leukocytes and (2) that they are a form of lymphocytes.

Normet, after much experimentation, concluded that the mononuclear leukocyte is capable of directly or indirectly producing an eosinophil cell and even red blood cells, and that it is the cell of origin of all the blood cells.[16]

The white blood cell is the most primitive, derived from the mesenchyme cell. The earliest blood cell discovered in the fetus is the white, and the red cells are probably derived from the white cells. The earliest heart was possibly a lymphatic heart, circulating white blood, which merged later with the venous heart, leaving among other evidence the lymphatic connection of the thoracic duct with the venous system. Animals which have only one kind of blood have white blood. The fetal blood cell is produced by the lymphoid and adenoid structures of the body, including the liver and spleen.

Classification of Spleen Functions.

1. Blood formation.
2. Blood destruction.
3. Role in iron metabolism.
4. Regulating influence on blood-producing organs.
5. Function concerned with digestion.
6. Cholesterinogenic function.
7. Internal secretion of the spleen.
8. Detoxicating function.

Blood Formation. There is no doubt that the spleen is a leukopoietic organ. The studies of the venous blood of the spleen and especially its white-blood-cell content lend support to our knowledge of its blood-forming function.[17] The venous blood of the spleen shows many more (seventy times as many) white blood cells than the splenic artery and many more than the vein of any other organ of the body.[18] This abundance of white blood cells occurs especially a short time after a meal. The number of polynuclears is greater in the splenic vein than in the artery, whereas a larger number of mononuclear cells are brought by the artery.[19]

Ehrlich obtained definite data of the influence of splenectomy on the white blood cells. He concluded that the spleen of the guinea-pig plays a subordinate role in the production of white blood cells.[20] Its absence is compensated for by the function of the lymph glands. The characteristic change is an increase of eosinophil cells the second year after splenectomy, and lymphocytosis during the first year. Audibert and Vallet,[21] Port,[22] and the recent work of Dubois[23] accord with these results, as also do the findings of Noguchi[24] and Bayer[25] in a case of splenectomy in man.

The focus of origin of the lymphocytes is the spleen follicle. They circulate from here through the red pulp together with the blood. The presence of myelocytes in the spleen suggests the possibility of their origin there; if not normally, under pathologic conditions.

Blood platelets are not present physiologically in the liver, lymph glands or bone-marrow, but they are in the blood channels of the spleen. Following splenectomy a remarkable increase of these elements takes place in those organs. This speaks for the seat of normal production in the spleen, a function which the organs take on vicariously.[26] There has been found a transitory but distinct increase in the blood platelets in the circulation following splenectomy.

In certain conditions, after many infectious diseases, in anemia and in some other pathologic conditions, changes take place in the spleen pulp and in the interfollicular regions that resemble myelogenous leukemia. Ehrlich[27] first described this and found that when blood crises took place the bone-marrow elements were held

back in the spleen where they underwent proliferation, thus essentially acting as metastases from the bone-marrow. This myeloid tissue is more abundant in the embryonic spleen and it is conceivable that the rudiments of this take on sudden growth under a special stimulus in the above conditions.[28]

The thickness of the capillary walls of the spleen is greater than in any other vascular organ, and they are supplied with nerves, implying a close association of the organ with the vegetative nervous system.

Elliott and Kanavel[29] have shown that the intramuscular injection of epinephrin contracts the spleen one-third size. According to Hartmann and Lang,[30] dilatation of the spleen is caused by the action of epinephrin on the twelfth and thirteenth dorsal root ganglia, the semilunar ganglion or on some terminal structure in the spleen itself. Constriction can result from the response of a mechanism in the dorsal root ganglia or from a structure in the spleen.

Frey's[31] adrenalin test for the hemopoietic function of the spleen consists of a subcutaneous injection of 1 mg. of adrenalin. Normally after twenty minutes a distinct increase of the leukocytes in the peripheral circulation takes place with particular increase of lymphocytes, *i. e.*, a relative lymphocytosis. There may be a still further increase in one hour. In disease of the spleen, especially in Banti's disease or fibroadenie of the spleen, the increase of leukocytes is slight or absent, with no relative lymphocytosis. This reaction is negative after extirpation of the spleen in dogs.[32]

Sanguinetti[33] does not agree with the hypothesis that the increase in white blood cells after adrenalin comes in large degree from this organ. The same dose of adrenalin will in one case produce contraction of the spleen and in another none, although in both cases the increase of white corpuscles in the circulation is nearly doubled. A better hypothesis, according to him—based on observations showing that cold increases the leukocytes while the heat scatters them—is that the increase after adrenalin must be ascribed in large part to changes of capillary circulation. For the present it must be believed that the properties of the blood elements themselves, such as specific gravity and viscosity, determine their special distribution in the capillary regions. This belief is strengthened by the cell modifications and the changes of leukocyte formulæ occurring in the veins and capillaries produced by adrenalin.

Freidberg[34] finds no effect on the white blood cells of children upon stimulation of the vegetative nervous system. He finds a marked similarity between the pilocarpin and the epinephrin blood pictures which leads to the supposition that these blood reactions are not dependent on the specificity of the ingested drugs but are rather a general form of reaction of the hemopoietic organs to nonspecific stimuli.

It has been written[35] that the visceromotor centers in the cord may be stimulated by percussion so that one may at random either contract or dilate the spleen. These reflexes are known respectively as the splenic reflex of contraction and dilatation. Normally the reflexes are of short duration, not in excess of two minutes. It has been determined empirically that the excitation of the reflex of contraction is effected by concussion of the second lumbar spine and the countersplenic reflex of dilatation by concussion of the eleventh dorsal spine. A pleximeter is placed on either spinous process and then struck a series of moderately vigorous blows with a plexor.

The attempts of Scalas[36] to elicit the splenic reflex in 9 children and 10 adults were practically negative. After percussion of the spine in 5 children there was a slight increase in mononuclears and transitional cells in the blood. But in no instance was a febrile attack elicited in malarial cases, nor did the parasites appear in the blood.

Blood Destruction. Eppinger[37] summarizes the theory of spleen function so far as it concerns blood destruction somewhat as follows: There is a double way open for the red blood cells after entering the splenic artery to gain entrance into the pulp structure. One way is through the pulp artery of the spleen sinus and the other way is directly into the pulp along unchannelled paths. Those which go the first way leave the spleen unchanged; those, however, which go the second and invade the tissue are probably ripe for degeneration to take place and, after more or less time in the pulp, are destroyed. Those of these, however, that find their way into the sinus perhaps later become destroyed by the macrophages. The pulp substance serves, therefore, as a place where the red blood cells are discarded and undergo destruction and phagocytosis by the macrophages.

One normal function of the spleen, therefore, is the capacity for selection of which red blood cells are to undergo destruction and which are to continue in the circulation. They may be somehow injured by the contact with the spleen tissue and continue to suffer degeneration in their course through the liver.[38]

Von Kölliker[39] showed that the red blood cells undergo changes immediately on entering the parenchyma of the spleen. They become smaller, darker staining, and finally break up into small granules. He expressed the belief that this constituted physiologic pigment metamorphosis of the red blood cells.

Virchow[40] showed that phagocytic cells containing red blood cells and pigment exist wherever there is extravasated blood, and also in chronic inflammations, in the lymph glands, the bone-marrow and after blood transfusion. Perls[41] by a staining reaction definitely proved the iron content of these cells. Metchnikoff[42] later definitely established the phagocytic power of these cells and called them macrophages, laden as they were with red blood cells.

These have been believed to be destructive of the red blood cells and capable of decomposing their hemoglobin.[43 44]

The spleen loses its power to produce red blood at birth and the liver at about the fifth fetal month, but the spleen retains its power for a limited production of white cells throughout its life. This is shown by a relative increase in the white cells and hematin in the splenic veins over other veins in the body.

The spleen also assumes the function of the destruction of worn-out red cells. This function depends upon: (1) An active cellular change, such as phagocytosis; and (2) a chemical change as by means of lysis, or by diminution of the resistance of the red blood cells to lytic influences. It seems that a cellular function of the spleen predominates in its blood-destroying mechanism.

Some investigators hold that phagocytosis is of itself sufficient to account for blood destruction. The spleens of different species show that this function is subject to wide variation. The number of corpuscles ingested in the large spleens of the rat, dog and guinea-pig is so considerable that, *a priori*, one might suppose phagocytosis to be the means whereby in these creatures the destruction of erythrocytes is accomplished. But in the cat phagocytosis does not come in for consideration; in normal man, the monkey and the rabbit it cannot be held responsible for the disappearance of any important amount of blood.[45]

The erythrophages apparently attack only injured red blood cells, being particularly abundant after the intravenous injection of distilled water. They serve not alone the purpose of phagocytosis of red blood cells in the spleen but carry these cells to the liver and thereby subserve a function in the process of blood regeneration,[46] or, as Gerlach and Schaffer[47] called it, "endogenous blood production."

It does not seem likely that the normal spleen possesses or produces any hemolysin comparable to the hemolysin *in vitro*. After splenectomy the resistance of the red blood cells to hemolysis increases.[48] Experimentally it reaches its height two months following splenectomy and maintains it for a varying time, even after one year.[49] The erythrocytes of the splenic vein show a lower resistance than those of the splenic artery.[50] This fact is conspicuous in support of the hemolytic power of the spleen.[51 52]

However, nowhere have hemolyzing cells or red blood cell shadows been found. This is evidence that hemolysis in the gross sense does not occur. Instead, another and unsuspected method of blood destruction has been found in the cat, rabbit and dog, namely, disintegration of the cells by fragmentation without loss of hemoglobin while they are still circulating. Extracellular blood destruction produces in the spleen accumulations of microcytes and poikilocytes such as are met with in the circulating blood. The shape of these in the peripheral blood and spleen is to some extent peculiar to the

animal species. This constant presence in the spleen of an accumulation of poikilocytes which are subdividing, and of microcytes, and the presence of these elements in the circulating blood indicate that the red cells disappear, in part at least, by fragmentation.[45]

Ehrlich long ago found that the microcytes and poikilocytes of anemia result from fragmentation of the circulating cells while in the blood stream. He based his view on the fragmentation *in vitro* of red cells under the action of various physical and chemical agents. Ehrlich named these true fragmentation forms "schizocytes." Large numbers of the fragments accumulate in the spleen. Many, though, circulate for a greater or less time. In normal and plethoric animals the accumulation of schizocytes in the spleen is striking.

That this organ has some important function in connection with such elements cannot be doubted, and the findings in plethoric animals suggest that the bone-marrow may share the function if blood destruction is great. When human beings are severely burnt many red cells break into hemoglobin-containing fragments. These collect in the spleen so rapidly that within a few minutes practically all are removed from the blood. Not improbably the blood of normal and plethoric animals is kept free of fragments in much the same way. They are not taken so completely from the blood of anemic animals. Perhaps a change in the protoplasm, such as may be thought to accompany normal aging of the cell, is necessary for this. But even in anemia microcytes and poikilocytes accumulate in the spleen to a noteworthy extent.[53]

A constant rapid fragmentation of the effete red cells, one by one, while still circulating, and a prompt utilization of the products of destruction will readily account for the high general standard of cell resistance. Whether, indeed, as the red cells fragment, their resistance lessens, as determined by the ordinary tests, remains to be determined. The fragmentation does not involve a loss of hemoglobin, and, *a priori*, there is no reason why it should be accompanied by a decreased resistance to hemolysins or hypotonic fluids, the ordinary test agents.

Frey[54] reports experiments which show that the blood from the splenic vein contains fewer erythrocytes than the arterial blood or the blood from a vein in the ear. This difference becomes larger after the resistance of the red corpuscles has been reduced by a blood poison, such as during ether anesthesia. The difference grows less and less when the resistance of the red corpuscles is enhanced by substances such as phenylhydrazin. The hemoglobin percentage is alike in both splenic vein and ear vein blood in dogs. As there are fewer erythrocytes in the splenic vein, this finding in regard to the hemoglobin seems to suggest that free hemoglobin is present in the serum of the blood in the splenic vein, an observation also made by Banti[55] and Furno,[56] but not confirmed by Krumbhaar and Musser.[57]

Gilbert[58] believes that a close relationship exists between the loss of splenic function and the appearance of nuclear particles in the blood. These occur in large numbers within a few hours after the removal of the normal spleen, and continue to be present after the blood has become in other respects normal. They occur independent of any primary blood disease. In no other conditions are they found with such constancy and in such large numbers as after splenectomy. There is no definite numerical relationship between the nuclear particles and the presence of the true nucleated red cells or any other quantitative or qualitative changes in the peripheral blood. They originate from otherwise normal nuclei and do not show in themselves a qualitative degenerative process.

Benda[59] described so-called "tingible" bodies in the spleen which he believed to be phagocytosed and degenerated leukocytes. That the leukocytes are destined to undergo changes in the spleen analogous to the erythrocytes is conceivable.

The number of red blood cells per cu. mm. of blood is equivalent to the number of red blood cells produced minus the number destroyed. (Red blood cells in circulation = P.—D.) This, Eppinger[60] calls "Blutmauserung." The same would hold for the hemoglobin production and destruction.

Relation of Spleen Function to Blood Destruction and Jaundice. The natural life of the erythrocytes has been estimated at from ten to fourteen days. This estimate has been made largely on the assumption that biliary pigments are derived entirely from the destruction of erythrocytes. Recent experiments throw considerable doubt on this view. It is therefore quite probable that the life of the red cell is much longer than has been estimated.[61]

Pugliese[62] found a marked lessening of the amount of bile obtained through the biliary fistula following splenectomy, and concluded that the function of the spleen is to gather deteriorating red blood cells and transport them to the liver for destruction. Eppinger[63] believes that the amount of bile produced before and after splenectomy depends upon its original hemolytic functional activity. If the function is prominent in the spleen, the amount of bile pigment after splenectomy will be less.

When hemoglobin is set free in the portal circulation, a larger amount is held by the liver and converted rapidly into bile pigment than is the case when it is set free in the general circulation. Under the former condition, overloading of the liver with bile pigment more readily occurs and jaundice is more apt to develop. This mechanical influence accounts for the lessened tendency after splenectomy to the jaundice which follows blood destruction due to hemolytic agents. Whether the spleen be an active factor in destroying the erythrocytes, or whether it plays merely a passive part as a place for the deposition of the disintegrating cells, there can be no question that in this organ, when it is present, a large

number of cells undergo their final disintegration after the action of hemolytic poisons. The hemoglobin there liberated passes by the portal system directly to the liver. When the spleen is removed this disintegration occurs in other organs, notably in the lymph nodes and bone-marrow, and the hemoglobin from these organs passes not into the portal but into the general circulation, from which it reaches the liver more gradually and in a more dilute form.[64]

Animals whose splenic blood supply has been diverted from the liver into the renal vein or inferior vena cava show a lessened tendency to jaundice similar to that exhibited by splenectomized animals receiving hemolytic serum. The lessened tendency to jaundice is, in part at least, due to a mechanical factor dependent on the course of the blood supply to the liver.[65 66]

In hemolytic jaundice there is excessive fragmentation and destruction of blood in the spleen-liver system because the circulating erythrocytes are usually fragile. There is, however, no bile in the urine, but bilirubin is found in the blood, urobilin in large amounts in the stools and the urine, and the bone-marrow shows signs of hyperfunctioning. This disease may in one member of the family cause merely enlargement of the spleen, without jaundice or much anemia; another may have the enlarged spleen, anemia and urobilinogenuria but no jaundice, and a third may have all of these. The enlargement of the spleen may be a work-hypertrophy. The jaundice is no index of the gravity of the condition. The same symptoms characterize the type which develops without any known inherited tendency. The exacerbations may resemble gall-stone trouble, and the anemia may assume the pernicious type during the exacerbations; they are inclined to be more abrupt in the acquired than in the familial type.[67]

In all these hemolytic groups the removal of the spleen has proved the means of curing most, if not all, of both subjective and objective disturbances; only occasionally the red cells may still display a certain fragility.[68]

Hijmans van den Bergh applied the diazo reaction for a fairly exact determination of bilirubin in the blood serum (it is not present in the corpuscles). Among other important results he found that bilirubin reacts in different ways, according to whether its increase is due only to a mechanical obstruction or to other causes. The bilirubin of the mechanical icterus reacts with the diazo reagent in the uncoagulated serum (direct reaction), is largely adsorbed by the coagulated proteins and is oxidized and excreted more readily than bilirubin of the other group. The second group gives the reaction only when the serum proteins have been coagulated by alcohol (indirect reaction). This he calls "dynamic icterus."[69] The question of dissociation between the elimination of bile pigments (bilirubin and urobilin) and of bile salts is of the greatest importance. Both are found in the urine in cases of mechanical

obstruction to the outflow of bile. In hemolytic icterus only bile pigment is present (urobilin). In a third—the greatest—group of cases attributed to hepatic insufficiency both bile pigments and bile salts can be present in the urine.[70]

Jaundice in the newborn cannot be attributed to mechanical stasis, for it gives the indirect reaction. The formation of bilirubin in the spleen in pernicious anemia and in some intoxications has been proved directly by comparison of the amount of bilirubin in the vessels. The question whether bilirubin can form outside the liver (also in extravasates) is definitely settled in the affirmative.[71]

Role in Iron Metabolism. In 1834 Johann Müller[72] first showed the existence of iron-containing pigment in the spleen, which von Kölliker[73] and Ecker,[74] in 1847, showed to be present in the pigmented cells.

The spleen is one of the richest iron-containing organs and is a storehouse for the iron which is liberated from the decomposition of the blood tissues. The liver, on the contrary, is the storehouse of the iron ingested, but may partake of the splenic function.[75] Tedeschi[76] found that after splenectomy the liver and bone-marrow become richer in iron and give histological evidence of the increased iron content.

The iron output following experimental splenectomy or roentgen ray of the spleen is much greater than normal. It must therefore be considered that the spleen contains nascent iron, controlling both the exogenous and endogenous iron, since the increased output maintains both in hunger and on meat diet. The increase of output is still found eleven months after the operation.[77]

Experimental plethora can be produced by injecting defibrinated blood in splenectomized animals. The blood picture returns to normal the same as in normal controls. The anemia following poisons is recovered from also the same as in the normal. If the diet is iron-free following splenectomy anemia develops more promptly than on the normal diet; while on iron-rich diet the red blood cells increase.[78] Feeding iron in normal animals increases the iron of the spleen macrophages and of the liver Kupffer cells as well as of the kidney cells. Following splenectomy the preponderance of iron is in the liver cells and also in the epidermis.[79]

Chevalier proposed the following theory of the function of the spleen in relation to iron metabolism. He believes that the source or origin of the iron conditions its distribution in the body and its output. He thus speaks of an excretory tissue and an assimilative tissue. The skin, liver and kidney epithelium he places in the first class as excretory tissues; the macrophages or Kupffer cells of the spleen and liver and the endothelial cells of the skin and interstitial perivascular cells belong to the assimilative group. These he names siderocytes.[80]

On this basis the spleen has the function to: (1) Serve as a

storehouse for siderocytes and (2) to stimulate the activity of siderocytes in other organs of the body. It thus serves as a controlling organ for the entire siderocyte system. If the spleen fails in the latter function the iron-storing property of these cells is also lost. The spleen removed, the siderocytes partly take on its function, at the same time storing iron for the economy of the organism. If the siderocyte system fails, as it often does after splenectomy, the iron output is increased in the excretory cells.

Blood destruction due to a single injury, as by sodium oleate acting through a short period of time, or by toluylenediamin or hemolytic immune serum, as well as the continuous blood destruction of essentially a chronic experimental anemia, caused by infecting the dog with Trypanosoma equiperdum is not characterized in the absence of hemoglobinuria by an increased elimination of iron in the urine or the feces. This evidence of the power of the body to conserve the iron resulting from erythrocytic disintegration is further emphasized by the increased storage of iron in the liver and spleen.[81]

In view of this definite evidence of the power of the animal body to conserve iron, it is obvious that in the hemolytic anemias in man characterized by excessive elimination of iron in the feces some other factor than mere blood destruction is operative. Theoretically, it may be assumed that it is a disturbance of the mechanism concerned in the retention or conservation of iron.

Regulating Influence on Blood-producing Organs. Krumbhaar, Musser and Pearce[82] believe that the spleen has a stimulating influence on the blood-forming organs, since anemia due to bleeding or hemolytic poisons recovers with much greater difficulty and slowness in the splenectomized than in normal dogs. Eppinger concurs in this belief.

The lipoids and cholesterin in the blood increase with hemolytic anemia as after toluylendiamin and the blood regenerates quicker, possibly because of the presence in the circulation of the material for regeneration by the bone-marrow. The iron, besides, may also stimulate the bone-marrow. This occurs also after injection of erythrocyte lipoids, but not after posthemorrhagic anemia. The spleen possesses these iron-containing lipoids and nucleoproteins, and its function as a stimulant of the bone-marrow may depend upon these. The administration of spleen subcutaneously and intraperitoneally produces an increase in the red blood cell count, perhaps by an organic stimulus to the bone-marrow.

Gilbert[83] found a tremendous bone-marrow stimulation immediately after splenectomy in two patients, as evidenced by the marked leukocytosis, the increased nuclear red forms and increase in the large mononuclear and transitional groups. One year later the differential count was very much the same, except for the increase in the lymphocytes and the marked increase in the number

of nucleated red cells. It would seem that the spleen has a very definite relation to bone-marrow cell production and to the maturing of the red cells, especially in the destructive metabolism of their nucleus. After a definite remission in these two patients there was much greater evidence of hemolysis than before. The bone-marrow in both cases showed marked activity, the principal change being the large number of normoblasts and of all stages in the formation of nuclear particles.

Brinchman's[84] experimental work also shows that in some indirect way the spleen exerts a regulating influence on the blood-producing organs, steadying the factors which direct the normal production and destruction.

Freytag and Eppinger[85] have shown an increase of the red blood cells following splenectomy and concluded from that fact that the spleen has a regulating function on the bone-marrow, inhibiting its production of red blood cells. Frank[86] believes that it is a hormone produced by the spleen that stimulates the bone-marrow.

Stradomsky[87] seems to have demonstrated that the spleen has a two-fold hormone action on the bone-marrow, an inhibiting action on the production of red corpuscles in the bone-marrow, and at the same time a stimulating action to increased destruction of these cells. Normally these two influences balance each other, but when the spleen hormone is abnormal or lacking the bone-marrow produces unlimited quantities of red cells; but their quality deteriorates. They die off more readily, and this increased erythrocytosis sets up an automatic vicious circle. Among the facts on which these assumptions are based are the increased numbers of red corpuscles found in the blood stream after splenectomy, the number rising in the course of one, four to six weeks after the removal of the spleen, while almost at once afterward the red corpuscles present Howell-Jolly bodies, showing that these erythrocytes are young immature forms.[88] [89]

These findings indicate that the bone-marrow is functioning to excess after having been released from the controlling influence of the spleen hormone. After splenectomy, administration of spleen extract is liable to give results confirming this role of the spleen as a regulator of blood production. Another argument in favor of this assumption is the atrophy of the follicles in the spleen to which Hutchinson[90] and others have called attention in cases of polycythemia. It might be objected that polycythemia would follow in every case of disease of the spleen, but the diversity of pathologic conditions in the spleen may leave some parts of the organ intact, at least enough to produce sufficient of the hormone to prevent excessive production of red blood cells. There is also a possibility that the bone-marrow may not respond in every case in the same way.

The reason for the inconstant results as to the increase of red

blood cells following splenectomy is explained by Eppinger[91] by the original condition of the spleen. If it be rich in blood before removal the effect on the erythrocytic blood picture would be different than if the red pulp be deficient in red blood cells.

Following removal of a ruptured normal spleen, Hall[92] found a considerable increase in the total leukocyte count which persisted with much irregularity for over three months. In the early period all types of leukocytes were increased in nearly the same proportion. This period represents the effect of removal of the spleen on the organs of blood formation and destruction. In the second period both total and differential counts showed such marked variation as to render averages valueless, but the total count was usually high. This period, lasting about two months, was one of adjustment of the organism to the new conditions while other tissues were possibly taking over the functions of the absent organ. In the final period a comparative equilibrium was reached, with a moderate increase in the total count, due entirely to lymphocytes and endothelial cells, while the granular leukocytes showed strictly normal figures.

The immediate increase of all cells after operation suggests the removal of some factor that either restricts production of white cells or destroys those that have passed their usefulness. In the Arneth index we have for the neutrophils a means of estimating which factor is mainly concerned. In the first period in this case the index was very slightly increased. As the neutrophils were present in more than double normal numbers it seems probable that the increase was not entirely due to lessened destruction. Moreover, the coincidence of a rise of the index with the first sharp drop of the neutrophils at the beginning of the second period, the fact that during this period high points in the neutrophil curve tended to coincide with high points of the index, and that the index remained high with a normal number of neutrophils in the final period, all suggest that the variations in the cell count are due at least in part to variations in the number of cells produced rather than to changes in the rate of destruction. This point of view would result in the conception of the normal spleen as exercising a restrictive action on the production of the leukocytes.

It has been proved experimentally on normal animals that the spleen and the lymph nodes are the most sensitive organs in the body to the action of radium and roentgen rays. A few hours after the radiation of a normal animal there is noticed destruction of the cells of the lymphoid tissue and the spleen.

Cases of myeloid leukemia given a brief and mild course of roentgen-ray treatment of the spleen have shown the blood count to return practically to normal. This suggests that the spleen may have a special function in some circumstances, manifested by an inhibiting and impairing of the functioning of the bone-marrow. This special function seems to be set in action by the influence of certain morbid processes in the spleen itself.[93]

Function Concerned with Digestion. The exact role of the spleen in digestion is not known. The theories proposed are that:

1. The spleen gives to the blood stream during digestion a substance which activates or leads to the further elaboration of the gastric enzymes, especially pepsin.

2. The spleen is a storehouse for the temporary reception of the products of protein digestion, much as the liver is for glycogen.

3. The spleen is merely a diverticulum of the portal system to receive the excess blood rushed to the splanchnic area during the digestive period and to act as an abdominal heart for supplying this blood to the stomach and other abdominal organs as needed.

The idea that the spleen must be of some significance in this regard has been prompted by the gland's intimate anatomic connections with the portal system; its blood supply from the celiac axis; its marked congestion and swelling observed during the digestive period, with a gradual resumption of its normal size after several hours; its proportionately excessive atrophy during starvation and inanition; and by references by many experimental investigators, as well as many clinicians, to a state of hunger and voracious appetite after splenectomy.

The pepsinogenic function of the spleen has, indeed, often been mentioned as a possibility of physiologic importance. Tarulli and Pascucci[94] carried out a set of experiments on dogs in which they determined the digestive activity of the gastric juice before and after splenectomy. They concluded that during gastric digestion the spleen elaborates a pepsinogenic substance which is carried to the gastric glands through the blood stream and induces an increased amount of pepsin secretion. Gallenga[95] found increase in activity of the pepsin of the gastric filtrate from a splenectomized patient in artificial digestion by the addition of an extract of lambs' spleen, and concluded that this action of the spleen must depend on a pepsogenic internal secretion.

Trampedach[96] arrived at the conclusion that extirpation of the spleen has no diminishing influence on the digestive power of the stomach.

Recently, Inlow[97] studied the gastric secretion of animals under carefully controlled conditions before and after splenectomy, and concluded that a definite pepsinogenic function of the spleen has not been demonstrated and that the relation of the spleen to gastric secretion is probably merely vascular, the diminution in the amount of the juice secreted after splenectomy being attributable to decreased gastric blood supply from injury to the gastrosplenic circulation.

Cholesterinogenic Function. King,[98] Eppinger[99] and Denis[100] each found that there occurs an increase in the total fats and cholesterin in the blood after splenectomy.

Abelous and Soula,[101] during research on the action of the spleen,

have made the new observation that the injection of dilute hydrochloric acid into the duodenum produces increase of cholesterin in the arterial blood. This does not take place in splenectomized animals. From this they concluded that the spleen possesses a cholesterinogenic function and that the liver possesses this function only to the very slightest extent.

Internal Secretion. It has repeatedly been alleged that the spleen is an endocrine organ with the function of influencing, in an obscure manner, some portion of the digestive apparatus by way of the blood stream or of activating one or more of the digestive enzymes by an internal secretion.

The hypothesis that the spleen produces an internal secretion is supported by: (1) The changes in the erythrocytes after splenectomy; (2) the modification of the blood picture in hyperplasia of the spleen, ameliorated in the same cases at least by splenectomy; and (3) the specific effects on the red blood corpuscles of injection of splenic extract. The chief function of the spleen is the removal from the circulation of the disintegrated erythrocytes; the splenic cells elaborate this material, producing from either the stroma or pigment portion an internal secretion. This internal secretion reduces the resistance of all the red blood corpuscles, the effect amounting to actual destruction of the older cells; and, finally, this internal secretion, possibly after modification by the liver, stimulates the erythrogenic function of the bone-marrow and is used up in the manufacture of new corpuscles.[102]

The presence of a spleen hormone to explain the lymphocytosis and the hypertrophy of the lymph glands following splenectomy was also proposed.[103] Krumbhaar[104] and his associates believe that a specific hormone of the spleen is activated by passage through the liver. Their experiments showed that the anemia which develops after splenectomy is more marked in animals on essentially a cooked, mixed diet than on a diet of raw meat. This suggests the possibility that heat alters the substance which, in the absence of the spleen, the body cannot utilize.

Reasoning hypothetically, Mayo[106] surmises that the spleen does not possess an internal secretion of importance, not only because removal of the normal organ does not disturb the body metabolism, but also because of its extremely limited sympathetic nerve supply. It is to be noted that the organs of primary internal secretion usually act through the sympathetic nervous system. The adrenals and the pituitary are so closely connected with the chromophil system that their union amounts almost to a single organ, half sympathetic and half secretory. Other organs, like the thyroid, gonads, pancreas, etc., which have internal secretion acting to a large extent through the blood stream, had at one time or still possess an external secretion as well as an internal.[105] The spleen does not properly fall into either of these categories.

On hypothetical grounds also it seems probable that the spleen develops certain enzymes which are important to its function, but it is equally evident that the function of the spleen is shared by other lymphoid and adenoid structures in the body, and that on the removal of the organ the function is continued by these collaborating structures.[107]

Kaznelson[108] has shown recently that the spleen possesses a thrombolytic function.

Although other investigators have shown that an enzyme or enzymes exist in the spleen capable of hydrolyzing peptone and also fibrin, Morse[109] found that the proteins of the spleen itself autolyze only in neutral or acid, not in alkaline solution. He suggests, therefore, that it is probable that the *a*-protease of Hedin is not an autolytic enzyme of the spleen but rather a heterolytic one resident in the white blood cells.

Detoxicating Function. The spleen is derived from mesoblastic tissue and is probably concerned largely with filtration of certain substances from the blood and the product of its activities is delivered to the liver through the splenic vein, suggesting at once what clinical experience has shown, a detoxicating function of the spleen.

Bacterial cultures were made of human spleens removed for surgical purposes. These usually remained sterile. In some instances the group of organisms found represented parasitic but nonpathogenic flora of the human body.[110]

Ozaki[111] found that the accumulation of bacteria in the spleen, such as occurs in experimental bacteremia, is principally dependent on the vital activity of the cells, and the mechanical filtration of bacteria by the spleen is not an important factor in their detention. He found that the spleen acts as a close filter for foreign erythrocytes, allowing very few to pass in dogs.

In typhoid fever the spleen becomes enlarged as a result of its straining function. The accumulated bacteria which have been strained out of the blood are sent to the liver for destruction. A failure in elimination of the bacteria from the spleen to the liver may result in multiple or single abscesses containing pure culture of typhoid bacillus.[112]

Enlargements of the spleen from chronic sepsis are not uncommon and may act as secondary distributing centers of infections.[113] Focal infections in various parts of the body may act as the primary source of the bacterial invasion. Septic endocarditis is a notable example.[114]

While tuberculosis of the spleen is considered by some observers as never primary, this condition has occasionally constituted the only known focus in the body.[115]

Spirochetal hibernation in the spleen is not unusual, and failure to eradicate the disease by arsphenamin and prolonged mercurial treatment may result in a syphilitic spleen which permits not only

luetic reinfection of the body but also causes a high grade of chronic anemia.[116]

It is probable that some form of chemotaxis attracts to the spleen all of these various agents.

The characteristic change following splenectomy, as Ehrlich has shown, is an increase of eosinophil cells the second year after removal.

The decrease of eosinophils in the peripheral circulation following starvation and the indications of a very close relationship between eosinophils and intestinal secretion suggest that the eosinophils may convey a hormone which is important for proper cellular activity in the intestine.[117] Their relation to anaphylaxis suggests that they are, in some measure, a reaction of the organism against the penetration of foreign proteins.[118] Eosinophils possess important phagocytic properties both for bacteria and cells and are well adapted to the absorption of toxic products and may play an important role in the maintenance of immunity.[119 120 121]

Giffin[3 122 123] reported a case of persistent eosinophilia with hyperleukocytosis and splenomegaly in which the spleen was finally removed. Examination of the organs four and a half years later showed eosinophilic polynuclears and myelocytes abundant in the bone-marrow and the abdominal lymph glands. In this case the permanent increase of the leukocytes following splenectomy for a period of four and a half years considered in connection with the occurrence of more or less constant eosinophilia after splenectomy for various other conditions may be indicative of some special function of the spleen with respect to eosinophilic cells or with respect to the toxins which eosinophilic cells are capable of absorbing.

The results recorded by Hektoen[124] show that splenectomy may diminish the output of antibodies, especially when done about the same time as antigen is injected. Antibodies appear earlier in the spleen than in the blood; antigen is fixed by the spleen and in the presence of antigenic substances cultures of splenic tissue outside the body may produce antibodies. The results of several experiments indicate, however, that after antibody production is well under way splenectomy has little or no effect on the course of the antibodies in the blood. The antibody content of the blood is not diminished markedly by splenectomy or roentgenization at or near the height of the curve. The nature of this so-called resistance remains obscure.

Effects of Splenectomy and Compensation for Spleen Function. We know that the removal of the normal spleen rendered necessary by traumatism, etc., introduces no serious bodily change.

The absence of the spleen has no influence on either the adult or the growing organism, and seems to be without influence on the mother or child if removed during pregnancy.[125] This holds for animals and for man. Henn[126] showed that the spleen is not

essential to the life of young rats, rabbits, kittens and puppies and that splenectomy has a negligible influence on their growth.

There seems to be no change in the general metabolic processes following removal of the spleen.[127] This holds for well-fed and poorly nourished animals, for the basal metabolism, carbon dioxide and sugar metabolism.[128] The spleen diminishes in size like the rest of the body with hunger.[129]

The fact, however, that the spleen can be extirpated without causing death or even considerable detriment to the animal organism does not militate against the conclusion that it is an organ of prime importance for the organism. Other organs (hemolymph nodes, bone-marrow and adenoid tissues in general) may assume part of the role of the spleen when this is absent, but only the severity of the blood-destroying agent and the individual resistance can determine whether the body can stand the strain when deprived of the spleen. Cases of death from removal of the malarial spleen indicate this strongly.[130]

After splenectomy the lymph glands of the greater curvature of the stomach and the omentum hypertrophy and become distinctly red, and new ones develop in the neighborhood of the extirpated spleen.[131] Hyperplasia of the lymphatics also gradually develops first in the vicinity of the portal vessels and then inside the liver lobes. This hyperplasia is evidently a compensating process in the lymphatic elements in the depths of the liver; it explains the increase in size of the liver which follows removal of the spleen.[132]

Schmidt[133] found iron-containing cells in the liver similar to the Kupffer cells, reminding him of spleen follicles. In these he found deteriorating red cells which he assumed developed to take on splenic function. The increase of Kupffer cells in the liver and changes in lymph glands and bone-marrow indicate a compensatory function on the part of these tissues in supplying a missing factor in blood formation and destruction.[134]

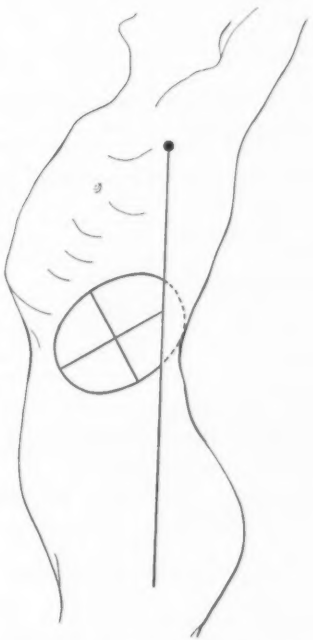
According to Freytag,[85] spleen function is fully compensated for within five or six weeks.

Physical Diagnosis of the Spleen. Palpation gives the only definite information as to the size of the spleen; if it cannot be felt, percussion is a poor and misleading substitute. We are as yet unable to study the earlier manifestations of associated diseases in relation to the size of the spleen, and its lesions are gross before we can be certain that it is concerned in the production of the symptoms from which the patient suffers.

To estimate more accurately the size of the spleen, Chauffard[135] draws a line from the middle of the axilla to the trochanter region, the arm held above the head. This line serves as the base from which the ovoid spleen is palpated and percussed, and the outline marked also on the skin. A line is then drawn from the base line axially to the farther limit forward of the spleen. This axial

line is bisected in the center by a line perpendicular to it. We thus have two lines that can be measured and compared from case to case, giving thus the approximate size of the spleen.

Radiographic examination of the spleen has been of comparatively little assistance in the diagnosis of its function. By means of the roentgen ray the outlines of the spleen may be fairly well determined. The examination is made, moving the patient from side to side so as to change the position of the adjacent hollow organs. The left costophrenic sinus indicates the position of the upper



Chauffard's Method of Estimating Size of Spleen.

pole and external surface of the spleen. Gas in the stomach or air introduced by tube may help in outlining the lower surface and right boundary of the spleen. In children who are easily moved about the outlines are more clearly defined. In pathologic spleens manifesting large tumors this method of examination, as well as insufflation of the colon with air, is necessary for differential diagnosis.[136 137]

Puncture of the spleen is attended with danger and is not practised clinically for diagnosis except in cases of suspected abscess.

Here the danger of infection is great and its use as a diagnostic method has been strongly opposed even in localized infections.[138]

Causes of Enlargement of the Spleen.[139]

I. In children.
   (*a*) Disturbances of metabolism, rickets, amyloid disease.
   (*b*) Chronic intestinal affections.
   (*c*) Large but ill-defined group of intestinal disorders, particularly in the tropics.
   (*d*) The pseudoleukemia infantum.

II. In the infections.
   (*a*) Syphilis.
   (*b*) Malaria.
   (*c*) Kala-azar and other forms of tropical splenomegaly.
   (*d*) Hodgkin's disease.
   (*e*) Tuberculosis.

III. In primary disorders of the blood-forming organs.
   (*a*) Leukemia.
   (*b*) Pernicious anemia.
   (*c*) Chlorosis.
   (*d*) Hemachromatosis.
   (*e*) Polycythemic splenomegaly.

IV. In cirrhosis of the liver.
   (*a*) Syphilitic.
   (*b*) Alcoholic.
   (*c*) Hypertrophic of Hanot.

V. Hereditary and family forms of splenomegaly.
   (*a*) Congenital acholuric icterus.
   (*b*) Constitutional disturbances, dwarfing, etc.

VI. Newgrowths and parasites.
   (*a*) Sarcoma.
   (*b*) Primitive endothelioma of Gaucher.
   (*c*) Echinococcus.
   (*d*) Schistosoma of Japan.

VII. Splenomegaly not correlated with any of the above or with any known cause.
   (*a*) Banti's disease with its three stages:
      1. Simple enlargement.
      2. Splenomegaly with anemia.
      3. Splenomegaly with anemia, jaundice and ascites.

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THE AUTOLYSATE–PRECIPITIN REACTION IN TYPHOID FEVER.

(A PRELIMINARY REPORT.)

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AND

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THE obvious necessity for improvement in the laboratory methods of diagnosis of typhoid infection and the failure of bacteriologic and direct immunologic research studies to accomplish it, has led us to seek a solution of the problem by an entirely new route. Research in typhoid determination has dealt almost entirely with attempts to discover more sensitive culture media for the differentiation of the nonlactose fermenting group as a first step in the diagnosis. Endo, Conradi-Drigalski, Teague's, malachite green, brilliant green and litmus media have been used and advocated by the various workers. All have shown results of about equal efficiency in the hands of their respective advocates. None has shown any appreciable advantage over the others, nor any advance in accuracy of differential diagnosis.

The reason for the failures to determine the typhoid bacillus in the excretions of typhoid cases and carriers by these methods, we believe to be twofold: (1) They depend upon bacterial action on lactose. This presupposes a goodly number of culturally typical typhoid bacilli in the stools and urine, a condition which probably rarely exists; (2) it is beyond reasonable doubt that many of the

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typhoid bacilli infesting the small intestine of the typhoid case are autolyzed during their passage through the intestinal tract, and, therefore, are not culturally demonstrable. Bacteriologic technic, under the most favorable conditions, will average about 25 per cent of positive results upon known typhoid excretions. The typhoid organism, even of the preëminently stable strains, such as Rawling's or Stewart's, so commonly used in the laboratories because of stability for agglutination tests, have been known to undergo mutation, to acquire the ability to ferment lactose. This has occurred several times in this laboratory, and has been verbally corroborated by other bacteriologists; the colonies showing marked fermentation having been identified as pure typhoid by other methods of determination. How much more likely, then, that this change in cultural characteristics should occur in the average unstable strain from the typhoid case. An examination by such method, therefore, fails in its first step.

It should be easily perceptible from the foregoing that one of three methods of attack must be adopted for improvement in typhoid determination.

1. To determine the typhoid bacillus by the other differential methods applied to all organisms present in the original culture of the excretions, regardless of their action upon lactose.

2. To employ a method of treatment to the excretions which will bring about a reclamation of the typhoid bacillus to cultural type before the application of the differential cultural methods.

3. To determine the presence of an autolysate of the typhoid bacilli in the excretions.

The first method is one appropriate to the more purely research laboratory. The second has shown some promise in this laboratory, in the use of the "living-culture tube" devised by Laird, the detailed description of which cannot be given in this article. This publication will deal entirely with the preliminary work upon the third method, the autolysate-precipitin reaction in typhoid stools and urine.

The autolysate-precipitin reaction should not be confused with the precipitin reaction heretofore employed in the diagnosis of typhoid.[1] Our reaction is dependent upon the determination of the existence of the autolysed typhoid bacilli in the excretions of the patient by means of a known specific typhoid rabbit's serum, in direct contrast to the older method which depended upon a precipitin reaction in the serum of the suspected patient by means of a known typhoid solution.

The technic of the autolysate-precipitin reaction was in part suggested by the promising work of Robinson and Meader upon the precipitin reaction in the diagnosis of gonorrhea.[2]

[1] Hiss and Zinsser. Text Book of Bacteriology, p. 424. Norris: Jour. Infect. Dis., 1904, **1**, 3.

[2] Robinson and Meader: Jour. Urol., 1920, **3**, 772.

Before entering into the actual procedure of our experiments the technic of preparing the serum and specimens will be described.

PREPARATION OF RABBIT'S SERUM (PRECIPITIN). *Method* 1. A suspension of typhoid bacilli is made, in N/00 NaCl, of two billion organisms per cubic centimeter and placed in the incubator for four days. It is then centrifuged and the clear supernatant solution used and kept at room temperature. One cubic centimeter is injected intravenously into rabbits at intervals of five to seven days for five injections; the rabbits are bled on the fifth day after the last injection.

The agglutination titer should be at least 1 : 1000 and the serum should show a definite precipitate with the original autolysate.

Method 2. One-hundredth of a twenty-four-hour agar slant of typhoid bacilli suspended in 1 cc of N/00 NaCl and killed at 60° for one hour is injected subcutaneously every seven days for five injections. The rabbits are bled on the fifth day after the last administration. The agglutination titer and the specific precipitation should be the same as No. 1.

Method 3. Injections of killed typhoid bacilli are given, first subcutaneously and then intravenously every day for nine days, according to the following table:

1st day	500	million	killed	bacilli	subcutaneously.
2d "	500	"	"	"	"
3d "	1000	"	"	"	"
4th "	1000	"	"	"	"
5th "	500	"	"	"	intravenously.
6th "	1000	"	"	"	"
7th "	1000	"	"	"	"
8th "	1000	"	"	"	"
9th "	1000, 1500, or 2000	"	"	"	"

depending upon the condition of the animal.

Allow animals to rest seven days, then make a test bleeding for agglutination titer and autolysate-precipitin reaction. Final bleeding is made upon the ninth day if tests are satisfactory.

All three methods have shown equally good results in the autolysate-precipitin reaction, but method 3 showed the highest agglutination titer, 1 : 6400.

PREPARATION OF THE INFECTED STOOL. Two grams of the stool from the typhoid patient are emulsified in 20 cc of physiologic salt solution (N/00 NaCl)* until a uniform suspension is obtained. A loopful of the suspension is placed upon a hanging-drop slide and examined for suspicious organisms. If any are present a portion is plated upon endo medium and incubated for eighteen to twenty-four hours. Suspicious colonies upon the plate are examined in

* Twenty cc of N/00 NaCl are used for the suspension because smaller amounts, due to absorption during filtration, yield an insufficient amount for the test.

the hanging-drop and transplanted to litmus milk and plain agar and incubated for twenty-four hours. Suspension is made from any growth upon the agar slants and the presence of the Bacillus typhosus verified by hanging-drop and specific agglutination.

While these routine examinations are being conducted the bulk of the original suspension is allowed to stand at room temperature until the insoluble matter has settled to the bottom of the tube, or, if the examinations have shown living organisms suggestive of Bacillus typhosus the suspension is placed in the incubator for twelve hours in order to insure sufficient autolysis. The supernatant liquid is then decanted and centrifuged for thirty minutes at 3000 r.p.m. The supernatant portion is again transferred to another tube and 0.5 gm. of Kieselguhr (diatomaceous earth) is added, agitated and filtered through filtering paper.

It was found that the above method yields a clear filtrate most suitable for our tests.

Preparation of Infected Urine. Before clarification for the tests the urine must be examined qualitatively for albumin, as it has been found that albumin causes precipitation with specific serum which might be falsely interpreted as a positive reaction. The other abnormal constituents of the urine do not influence the precipitin reaction. If albumin is present it is eliminated by adding dilute acetic acid, boiling until the albumin is precipitated and filtering. The resultant acidity interferes in no way with the precipitin test, but it may be neutralized to litmus with dilute sodium hydroxid solution. Moreover, we are led to believe that specimens infected with the Bacillus typhosus have a high degree of acidity which increases with the progressive autolysis. The determination of the actual hydrogen-ion concentration of these specimens has not been performed, but will be taken up in a later publication.

The specimen, free from albumin, is centrifuged for fifteen minutes or longer at 2000 r.p.m. to produce a clear supernatant fluid, to which Kieselguhr is added and filtered. Absolute clarity of the specimen is imperative, otherwise any sediment or cloudiness might be misconstrued as a positive reaction.

The controls for our experiments have been normal feces and urines treated under the same conditions as the infected specimens, together with direct controls of the latter to which no serum has been added and the unmixed serum.

Before performing the autolysate-precipitin test upon actual cases of typhoid, normal urines and stools were infected with Bacillus typhosus. (For this purpose a two-billion per cc suspension of Bacillus typhosus, Rawling's strain, was used.) The infected specimen was incubated for varying periods, six hours, twenty-four hours, four and seven days. Although we received positive reactions at the expiration of the incubation periods in all cases, it was

found that with increased autolysis there was increased precipitum. It was also found that the autolysate-precipitin reaction was consistently positive only with the specific serum: Other reagents used were mercuric potassium iodid, ammonium sulphate, ethyl alcohol and heat, but the varying degrees of accuracy eliminated them as possible precipitins.

It was observed, microscopically and culturally, that the Bacillus typhosus was appreciably lessened and the characteristics greatly altered after a long period of incubation, it being impossible to isolate the organism after four to six days. On the other hand, the autolysate-precipitin reaction became more marked.

TECHNIC OF AUTOLYSATE-PRECIPITIN REACTION. Specimens of the stools and urine were collected daily from the cases under our observation and prepared and examined as described under the separate headings.

The precipitin rack is set up, using three tubes for each patient. In the first and second rows place 1 cc of typhoid serum in each tube. To the first row add 1 cc of the specimen to be tested and slightly agitate. To the second row 1 cc of normal urine or extract of feces is added and the tubes agitated. In the third row 2 cc of the corresponding test specimen is placed and agitated. The tubes are allowed to stand at room temperature for one hour and then placed in the ice-box over night. In the morning the rack is again placed at room temperature for several hours.

At the expiration of four or five hours it will be noted that the solutions in the first row of tubes have become turbid or show appreciable precipitation in the positive cases. The second and third rows (controls) should be clear or contain a very small amount of precipitate due to deterioration, the supernatant solution remaining clear in contrast to the turbidity of the positive tests. Of course the specific serum control should accompany each set of tests and should remain clear.

Having observed satisfactory autolysate-precipitin reactions upon one hundred and fifty-two specimens of stool and urine from typhoid cases and convalescents, we deemed it advisable to perform the test upon autolysates of other pathogenic organisms occurring within the intestinal tract. For this purpose we used twenty-four-hour cultures of the following organisms: Bacillus morgani, Bacillus shigæ, Bacillus para coli and five strains of the Bacillus dysenteriæ-flexner (V, W, X, Y and Z),[1] together with Bacillus typhosus, Bacillus paratyphosus A and Bacillus paratyphosus B.

[1] Classification of the Dysentery-Flexner bacillus:
V = Oxford Flexner—Standard Laboratory—Old Flexner.
W = Cable, British Front, 1914 (new variety).
X = Hughes, Carrier, University War Hospital, Southampton (new variety).
Y = Original Hiss-Russell strain.
Z = Whittington, Carrier, University War Hospital, Southampton (new variety).

TABLE I.—AUTOLYSATE-PRECIPITIN EXPERIMENTS. NORMAL STOOLS INFECTED WITH B. TYPHOSUS.

No.	Feces, gm.	Sterilization.	B. typhosus 1 cc = 2 billion.	Incubation.	N/00 NaCl.	Incubation autolysis.	Hanging drop.	3000 r.p.m. centrifuge.	Hanging drop.	Reactions.			
										Typhoid serum.	Autolysate.	Immediate.	Time.
1.	1.02	30 minutes at 250° C.	1 cc	21 hours	10 cc	6 hours	++	30 minutes	±	0.5 cc	0.5 cc	None	Marked.
2.	1.40	30 minutes at 250° C.	1 cc	47 hours	10 cc	24 hours	++	30 minutes	+	0.5 cc	0.5 cc	None	Marked.
3.	1.35	30 minutes at 250° C.	1 cc	95 hours	10 cc	4 days	+	30 minutes	±	0.5 cc	0.5 cc	Slight	Very marked.
4.	1.20	30 minutes at 250° C.	None	21 hours 47 hours 95 hours	10 cc	6 hours 24 hours 4 days	−	30 minutes	−	0.5 cc	0.5 cc	None	None.

++ = Many motile bacilli. + = Some motile bacilli. ± = Few motile bacilli. − = No motile bacilli.
The precipitin used to produce the reactions was undiluted typhoid serum (rabbit), titer 1: 6400.

Suspensions of the cultures were made in N/00 NaCl and diluted to contain approximately two billion organisms per cc. They were placed in the incubator for six, twelve and seventy-two hours and then centrifuged to obtain clear autolysates.

The reactions gave very encouraging results with the specific typhoid serum. The members of the typhoid group (Bacillus typhosus, Bacillus paratyphosus A and Bacillus paratyphosus B) showed clearly positive while the seventy-two hour autolysates of the other intestinal organisms were negative. Here again it was noted that the reaction upon the typhoid group became more pronounced with the increased autolysis. The seventy-two-hour autolysate showed almost immediate precipitation.

Table I shows the results of the increased autolysis upon the autolysate-precipitin reaction.

It can be seen from this table that precipitation becomes more pronounced with increased autolysis; the ninety-five-hour autolysate showing almost instantaneous precipitation, while the twenty-four and seventy-two-hour autolysates required twelve hours for the reaction to occur.

Table II illustrates the reaction carried out with specific typhoid serum upon other potentially pathogenic intestinal organisms in comparison to the typhoid group.

TABLE II.—AUTOLYSATE-PRECIPITIN EXPERIMENTS. SEVENTY-TWO-HOUR AUTOLYSATE.

Organism.	Incubation.	Centrifuged at 3000 r.p.m.	Reactions.	
			Immediate.	Time.
Morgan 1	72 hours	15 minutes	None	None.
Shiga	72 "	15 "	None	None.
Typhosus	72 "	15 "	Slight turbidity	Marked.
Para A	72 "	15 "	Marked turbidity	Marked.
Para B	72 "	15 "	Marked turbidity	Marked.
Para coli	72 "	15 "	None	None.
Flexner V	72 "	15 "	None	None.
Flexner W	72 "	15 "	None	None.
Flexner X	72 "	15 "	None	None.
Flexner Y	72 "	15 "	None	None.
Flexner Z	72 "	15 "	None	None.

Suspension of 2,000,000,000 organisms per cubic centimeter used in the above experiment.

It will be noted that the reaction is markedly positive with the typhoid group, including the paratyphoid bacilli, while it is negative with the other organisms.

Table III shows the results of the autolysate-precipitin reaction upon actual typhoid stools and urine in the progressive stages of the disease and upon carriers and normal specimens.

TABLE III.

Day of fever.	No. of specimens examined, 297.	Blood culture.		Widal.		Bacteriologic.				Autolysate-precipitin reaction.							
										Immediate.				Time.			
						Urine.		Stool.		Urine.		Stool.		Urine.		Stool.	
		+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−
1st to 7th	9	1	1	4	..	..	7	1	1	..	..	..	..	7	..	2	
8th to 14th	9	..	..	1	..	1	2	1	5	..	..	..	..	3	..	6	
15th to 21st	18	..	1	..	..	..	13	..	5	..	..	..	..	13	..	5	
22d to 28th	27	..	1	..	1	1	15	..	11	..	..	..	..	16	..	11	
29th to 40th	24	..	..	..	..	..	17	..	7	..	..	..	..	17	..	7	
41st to 60th	33	..	..	..	..	..	26	..	7	4	2	5	2	24	2	5	2
Carriers	32	..	2	5	1	..	19	5	8	..	..	..	..	19	..	13	
Normal (control)	152	..	..	..	..	..	105	..	47	..	..	..	..	..	105	..	47

The blood culture and the Widal reactions were, of course, not performed as repeatedly as the bacteriologic examination and the autolysate-precipitin reaction; nor were they performed upon every case. The specimens represented in this table were obtained from 9 typhoid cases, 5 convalescents, 2 carriers and 10 normal persons. Attention might be called to the fact that the bacteriologic examination upon specimens from the known typhoid cases was positive in only about 6 per cent, while the autolysate-precipitin reaction was positive in 100 per cent up to the fifty-sixth day of the disease, after which the two negatives were obtained. The reaction in all instances was clearly perceptible, read and checked by several workers, except during the late convalescent period as the final negative was approached. During convalescence, after two negative bacteriologic examinations of the stool and urine released the patient from quarantine restrictions, the autolysate-precipitin reaction remained positive for many days.

Summary. A brief discussion of the problem of typhoid diagnosis is given with the reasons leading to the present investigation.

Experimental autolysate-precipitin reactions and the technic of preparation of the reagents and performance of the test are described.

Autolysate-precipitin reactions upon autolysates of other intestinal organisms with typhoid precipitin showed negative results. The reaction was positive not only to the Bacillus typhosus, but to the paratyphoid A and B autolysate.

The autolysate-precipitin reaction showed clearly positive in all cases of typhoid fever and carriers up to the fifty-sixth day of the disease. The carriers were of many years' standing, one dating back eighteen years.

The bacteriologic diagnosis was positive in only about 6 per cent of known typhoid cases.

Conclusions. It seems reasonable to conclude even at this early stage of experimentation, that the autolysate-precipitin reaction is distinctly more sensitive and accurate than any of the previous methods of typhoid determination.

Inasmuch as the unknown quantity in the reaction is a direct chemical derivative of the typhoid bacillus (typhoid autolysate) a positive reaction must signify the presence of typhoid bacilli in the patient from whom the test excretions have been obtained. In other words, as long as the autolysate-precipitin reaction remains positive the patient is harboring living typhoid bacilli and is a potential menace as a typhoid carrier. The reaction does not depend upon any immune process in the patient, but upon the presence of the chemical constituents of the typhoid bacillus in the excretions and, therefore, should not persist after the subject is free from this infection.

The persistence of the positive reaction long after the negative bacteriologic examinations, upon which patients have been released from quarantine restrictions, indicates the advantage of its adoption as a better method of control of typhoid cases and carriers.

The result of the autolysate-precipitin reaction in the early stages of the disease gives promise of its usefulness in the field of diagnosis as well as control of typhoid. It also gives promise of usefulness in the accurate diagnosis of abortive and atypical cases of typhoid which have hitherto been so difficult to determine because of the evanescent character of the infection and the consequent absence of immunologic effect.

It should eliminate, also, the confusion encountered in the serologic diagnosis in cases which have received typhoid prophylaxis.

The distinct specificity of the reaction to the typhoid groups suggests its possibilities in the diagnosis of other intestinal infections with the use of precipitins specific to them.

It seems appropriate to make passing mention of the saving of time and expense in this as a routine method of diagnosis and control, if further experimentation prove its promising dependability.

It must be understood that the foregoing conclusions should not be interpreted as final, in consideration of the limited number of cases. Many pertinent questions arise which can be answered only by continued experimentation upon typhoid in all of its phases and upon the other diseases.

THROMBOSIS OF THE CORONARY ARTERIES, WITH INFARCTION OF THE HEART.

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Introduction. Coronary thrombosis with infarction of the heart as a clinical entity is a condition which is generally classed among the rarities of medicine. Indeed, it is considered so rare and of so little importance that most of the text-books of medicine fail to give it mention or perhaps dismiss it with a brief paragraph, while several of the larger systems of medicine ignore it altogether. It has even been said by a very eminent physician[1] that "there are no characteristic physical signs or symptoms by which thrombosis of the coronary arteries can be diagnosed." So at best it is usually looked upon as a terminal event, impossible to diagnose and therefore of little clinical import. The literature on the subject, moreover, consists for the most part of a very small number of case reports; no attempt has been made to study a large series of cases, confirmed by necropsy, so that a clinical picture might be constructed which would enable one to recognize the condition. It is little wonder then that the diagnosis is generally left for the pathologist to make.

As a matter of fact the condition is not a very rare one; it merely goes unrecognized during life. To account for this failure of recognition, in part at least, one needs only to consider the mode of death of the individuals who die from this cause. As a rule, death is sudden or follows a brief acute illness, so that many of the patients are never seen by a physician at all, or are only examined after death by a coroner. A few, however, survive the attack, and on their account it is of great importance that the condition be recognized and properly treated. Its recognition is of further importance because of the close resemblance of the condition to acute diseases of the chest or abdomen; not infrequently it has been mistaken for pneumonia, pleurisy, acute cholecystitis, pancreatitis or perforated gastric or duodenal ulcer, and undoubtedly some of the so-called "negative laparotomies" could have been prevented had the condition of the coronary arteries been duly considered before the decision to operate was made.

Until comparatively recent years the literature yielded nothing more than a few case reports, and no attempt had been made to correlate these. Indeed, from the time of William Harvey to

[1] Broadbent, Sir William H.: Heart Disease, New York, 4th ed., 1906, p. 324.

the latter part of the nineteenth century little or no progress was made in the recognition of cardiac infarction. Harvey, however, reported a case[2] which was almost certainly one of coronary thrombosis, although he did not interpret it as such. The interest of it makes it worth quoting: "A noble knight, Sir Robert Darcy, an ancestor of that celebrated physician and most learned man, my own dear friend Dr. Argent, when he had reached to about the middle period of life, made frequent complaint of a certain distressing pain in the chest, especially in the night season; so that dreading at one time syncope, at another suffocation in his attacks, he led an unquiet and anxious life. He tried many remedies in vain, having had the advice of almost every medical man. The disease going from bad to worse, he by and by became cachectic and dropsical, and finally, grievously distressed, he died in one of his paroxysms. In the body of this gentleman, at the inspection of which there were present Dr. Argent, then president of the College of Physicians, and Dr. George, a distinguished theologian and preacher, who was pastor of the parish, we found the wall of the left ventricle of the heart ruptured, having a vent in it of the size sufficient to admit any of my fingers, although the wall itself appeared sufficiently thick and strong; this laceration had apparently been caused by an impediment to the passage of the blood from the left ventricle into the arteries."

A number of cases have been reported since Harvey's time, and in many of them some new sign or symptom has been observed and emphasized by the author, so that after a number of years the literature furnishes most of the important facts about the condition, though in a somewhat scattered and noncorrelated form. Morgagni,[3] Heberden,[4] and Caleb Hillier Parry[5] were among the first to associate anginal pain with lesions of the coronary arteries, and, in more recent years, Leyden,[6] Kernig[7] and Pawinski[8] reported pericardial friction rubs following angina, but apparently they did not realize the significance of the sign. Gorham[9] reviewed the literature on this point and reported several cases of cardiac infarction in which a friction rub was heard, and, on account of the constancy of this finding, he emphasized it as one of the most important of the diagnostic signs. Huchard[10] called attention to the persistence of pain or the so-called *status anginosus*, while Krehl[11]

[2] Harvey, William: The Works of William Harvey, Second Disquisition to John Riolan, Junior, p. 127. (Printed for the Sydenham Society, London, 1847.)

[3] Quoted by Osler.[13]

[4] Commentations on the History and Cure of Disease, London, 1816, 4th ed., p. 302.

[5] An Inquiry into the Symptoms and Causes of Syncope Anginosa, Commonly Called Angina Pectoris, London, 1799.

[6] Ztschr. f. klin. Med., 1884, **7**, 459. Quoted by Gorham.[9]

[7] St. Petersburger med. Wchnschr., 1892, **17**, 177. Quoted by Gorham.[9]

[8] Deutsch. Arch. f. klin. Med., 1897, **58**, 565. Quoted by Gorham.[9]

[9] Albany Med. Ann., 1920, **41**, 109.

[10] Tome II, Paris, 1899, p. 128.

[11] Nothnagel's System, **12**, 535, 699.

described cases of coronary obstruction without pain and recognized the compatibility of coronary occlusion with life. In this country Dock[12] was one of the first to emphasize the possibility of diagnosing the condition before death, and, in 1896, he lamented the fact that the profession was so slow in taking up the study of the disease. He also observed that a heart, although extensively necrosed, "may continue to act for some time fairly well," and he was among the first to recognize the true relationship of pericarditis to the syndrome.

It is to Osler,[13] however, that we are indebted for the first real correlation of the clinical and pathologic findings. In his study, the material for which came from his private practice, he gave a very thorough discussion of practically every side of angina pectoris and reported several cases of coronary thrombosis. Allbutt[14] also recognized the condition and discussed at length the origin of the pain and the cause of sudden death in this disease. Herrick and his co-workers [15] [16] [17] [18] have made a very careful study of the clinical aspects of a few cases, and have written an excellent description of the clinical features of the disease which has added much to the present-day knowledge of the condition. Sternberg,[19] Englehart,[20] Obrastzow and Straschesko[21] and others have reported cases in the past few years, some of which will be referred to later.

This paper is based upon a study of 19 cases of cardiac infarction observed at the Peter Bent Brigham Hospital. As each case came to necropsy many of the symptoms and signs observed in the physical examination during life could be correlated with the postmortem findings, and from the data so obtained an effort has been made to construct a clinical picture which might make the diagnosis of the condition less difficult. These cases fall under the general heading of acute cardiac infarction, and for the sake of convenience they have been subdivided into two groups: (*a*) Those cases in which there have been no signs or symptoms of beginning cardiac failure and little or no evidence of an impaired circulation previous to the infarction, and (*b*) those in which there had been organic heart disease with symptoms and signs of long standing, and, previous to the obstruction of the coronary arteries, the clinical evidence of a failing heart muscle.

Etiology. The idea has gained prevalence as a result of the reports of most writers that the disease is almost always limited

[12] Notes on Coronary Arteries, Ann Arbor, 1896.
[13] Lumleian Lectures, Lancet, 1910, No. 1, pp. 697, 839 and 973.
[14] Diseases of the Arteries, Including Angina Pectoris, London, 1915.
[15] Jour. Am. Med. Assn., 1912, **59**, 2015.
[16] Ibid., 1918, **70**, 67.
[17] Ibid., 1918, **70**, 1887.
[18] Ibid., 1919, **72**, 387.
[19] Wien. med. Wchnschr., 1910, **60**, 14.
[20] Deutsch. med. Wchnschr., 1909, **35**, 838.
[21] Ztschr. f. klin. Med., 1910, **71**, 116.

to the upper classes. Osler emphasized this point and others have remarked on the fact that it was a disease rarely seen among hospital ward patients or groups of poorer people. The explanation of this belief is due undoubtedly to the fact that the majority of the cases recorded are from the private practices of the writers; for the same reason it has been called a disease of professional men or men accustomed to large business worries. Osler, for instance, speaks of the high incidence of medical men in his series, and gives a list of well-known names which includes John Hunter, Charcot, Nothnagel and William Pepper, all of whom died of coronary disease. In our small series, however, the disease has not been partial in its selections but has included among its victims clerks, machinists, housewives, and, among others, one man who gave as his occupation "Christian Science healer." Nor has the disease confined itself chiefly to men, as has been noted in most of the previous reports, for 9 of the 19 cases were in women. With one exception all our patients were over forty years of age, being mostly in the sixth or seventh decades.

A thorough search of the records of these patients did not reveal any factors which might play a direct role in the etiology of the condition. Heredity was dismissed at once, for there was only one instance of sudden death in a previous generation. Evidence of syphilis and rheumatic fever was naturally very carefully sought, in view of the close relationship of both these diseases to heart disease and of syphilis to lesions of the bloodvessels. But not one of the 19 patients gave a history of syphilis, and of the 13 whose Wassermann reactions were done, all were negative. Finally, the lack of any evidence of syphilis at the postmortem examinations enables one to say that that disease was not an etiologic factor in this series of cases of cardiac infarction. Rheumatic fever was also unimportant as a causative factor, for in one patient only was there a previous history of this disease, and at necropsy this individual was the only one whose heart showed an old endocarditis. One could likewise rule out other conditions such as diphtheria, pneumonia, scarlet fever, chorea, acute tonsillitis, nephritis and hyperthyroidism as important causative factors, for not one of them occurred in more than two of the patients. There was also no history of excessive use of alcohol, tobacco, tea or coffee.

Attempts to establish vascular hypertension as a factor in the disease met with difficulties. In 3 of our patients hypertension was known to exist before the appearance of any other symptoms referable to the cardiovascular system, while several other patients had an elevated blood-pressure upon entrance to the hospital. But it is evident, of course, that no direct relationship is established, though hypertension as an accompanying factor deserves more consideration in the future than it has received in the past. Every patient in this series showed some degree of arteriosclerosis, and

the final cause of the infarction in every case was coronary arteriosclerosis. The factors, therefore, which lead to arteriosclerosis play an indirect part in causing cardiac infarction.

Onset of the Disease; Symptoms. When one considers the end-result and terminal condition of the heart, and especially of the coronary arteries, he is surprised to find in many instances no previous symptoms referable to the heart, and in others only mild symptoms which certainly would not indicate the true state of the coronary arteries. Eight of the patients, for instance, had noticed dyspnea on climbing stairs or walking fast. In three of these the dyspnea was of a paroxysmal type, coming on suddenly after exertion and disappearing after a short rest—in other words, the sign of what McKenzie calls a senile heart. In six instances there were previous anginal attacks which had begun only a few weeks or months before the terminal attack. In contrast to this group, with few signs or symptoms of warning, is the group of four other patients who entered the hospital primarily on account of moderately severe cardiac decompensation or failure resulting entirely, so far as could be determined, from sclerosis of the coronary arteries. Two of this group had also had hemiplegias.

The onset of symptoms of cardiac infarction then is sudden and abrupt and may be the first sign to the patient of any trouble with his cardiovascular system. He may be enjoying practically normal health one minute and in the next be seized with an excruciating pain, or perhaps with extreme dyspnea. Or the onset may occur after a number of anginal attacks which, together with dyspnea, may constitute the only previous warnings of involvement of the coronary arteries. But with this latter type the patient recognizes instantly that his attack (indicative of the infarction) is unlike any that he has ever experienced before. In this group, with few or no previous symptoms, pain is certainly the most prominent symptom of the onset—sudden, sharp, knife-like, excruciating and constant as a rule. The pain may occur in the epigastrium, over the heart, under the lower end of the sternum or in all these and in other regions; it may radiate to the nipples, to the arms or to the abdomen, and to various other places. There are, however, other types of onset, such as sudden severe dyspnea usually associated with extreme weakness. One patient, for instance, who was seated in the house at the time of onset, was seized with a sudden dyspnea which was so extreme that he ran out of doors to get air.

Following closely upon the pain or dyspnea, at times occurring almost simultaneously, there may be nausea, vomiting and diarrhea. Generalized sweating, cough, hemoptysis, cyanosis, aphasia, delirium, collapse and coma were noted in some instances. The skin was usually cold, moist and of a characteristic pale, ashen color. It is very interesting to note the relation of physical activity to the time of onset of cardiac infarction, since some anginal attacks

seem to be brought on by exertion and at times by overeating. In 3 of the patients the onset of the symptoms of the infarction followed severe exertion while in 5 other instances the patients were at rest at the time. In only 1 did the signs and symptoms of coronary obstruction begin after eating, so that it seems safe to consider that the onset of cardiac infarction is unrelated to the taking of food and bears little relation to exertion as a causative factor.

The onset in the group of patients with signs and symptoms of antecedent cardiac failure is in marked contrast to the group just described. In the first place 3 of the 4 patients were irrational, so that the occurrence of pain could not be ascertained, and, in addition, dyspnea, edema and other signs of heart disease had been present for some time and in such degree as to mask the onset of the thrombosis of the coronary arteries. One of these patients, however, before becoming irrational had a sudden increase in dyspnea and weakness, and, in a second one, a sudden increase in dyspnea with cyanosis had been noted. In the fourth patient, who was rational until death, no pain was felt, but several days previous to her entrance to the hospital she had noticed a sudden increase in dyspnea and became cyanotic at the same time. It appears then that in those individuals with signs and symptoms of a decompensated heart muscle the onset of coronary infarction is apt to cause a sudden increase in these signs and symptoms. The patients in group 2 did not exhibit the gastrointestinal symptoms or the other signs and symptoms shown by group 1, or else their symptoms were so masked that they were not detected. The skin of these individuals, for instance, was cyanotic and did not show the typical pale, ashen hue which was so characteristic of the other group.

With many cases of infarction of the heart death comes with the onset and is instantaneous; some patients may live a few hours or a few days; a third group of individuals recover, become ambulatory and are able to return to light work.

There are many characteristic features about the pain of cardiac infarction. In the first place it is usually persistent once it has begun, lasting hours or days, and this feature, together with the distribution of the pain, has given rise to the term *status anginosus*. This stands out in contrast to the attacks of simple angina pectoris, where the pain is more apt to last minutes. In some instances there are temporary periods during which the sharp, intense pain may change to a dull ache in the same region, but it is apt to return to its previous state of severity. In other cases the pain may be intermittent with periods of complete absence. The pain may be precordial, referred deeply within the chest (substernal), especially under the lower end of the sternum or in the epigastrium. At times it may cover the whole upper abdomen, but usually when

abdominal it is located either in the epigastrium or in the right upper quadrant. When the pain occurs in this region in repeated attacks it may resemble very closely the colicky pain of certain acute abdominal conditions; when tenderness and muscle spasm are associated with the pain in this region the diagnosis is a difficult one. Points of radiation of the pain vary considerably, but in this series there was radiation from the precordial and substernal areas to one or both arms, sometimes to the upper arms only, at others to the finger tips, to the left side of the neck, through to the back, across to the right chest or around both sides of the chest. From the epigastrium the radiation was apt to be upward toward the precordium or to the region of the nipples. In several individuals the taking of food or drink and exertion made the pain definitely worse, while in others eating and moving about caused no discomfort. Quotations from some of the patients' descriptions of their pain are rather vivid in some of the more unusual types. One individual said, "It feels as though someone has a vise on the end of my heart and is gradually tightening it." Another said, "It feels as if a large stick had been forced into my chest (substernal), and it is pressing on everything else in there." Still another complained of a "constriction inside," while those with the epigastric type of pain usually complained of sharp, stabbing pains in that region.

The attitudes of the patients as they lay in bed presented a marked contrast to that of patients with acute abdominal or acute respiratory conditions. In the abdominal type of pain the patients are constantly attempting to protect this part and to lessen the pain by such changes in position as bended knees, flexed thighs or any position which relieves the muscular tension; similarly in acute conditions of the chest, as pleurisy, for instance, the patient is apt to lie upon the affected side or to assume postures which lessen the motion on that side. In patients with cardiac infarction, however, nothing of this sort is seen. They lie in any position or may be propped up in bed, but soon find that no relief is obtained by changes in position. The pain seems to be beyond reach.

In 10 of our patients the so-called *status anginosus* was present, but after several days there was a gradual decrease, and, in some, a disappearance of the pain; in 2 the pain returned after a week in severe form and death followed the same day. Relief was impossible to obtain, in some instances large doses of morphin failing to influence the pain.

Dyspnea was a prominent and almost constant feature, being present in 16 of our cases of cardiac infarction. It was the predominant sign and chief complaint of four of the patients who had no previous signs of cardiac failure, being of such a severe type that it was out of proportion to the other findings in the heart and lungs. One woman, for example, sat up in bed and literally gasped

for air, yet on physical examination the condition found in the heart and lungs did not seem to account for the extreme difficulty in breathing. This point alone should suggest the possibility of cardiac infarction. There were other patients in whom dyspnea was not a prominent sign, and, indeed, in some it appeared only after mild exertion, such as lifting themselves in the bed or similar mild exercise. Despite this frequency of dyspnea, however, only 6 of the patients were orthopneic, and 2 of these were in the group with cardiac symptoms of long standing. Observations upon the vital capacity of the lungs of 2 patients were made; in 1 the reading was 900 cc, or 22 per cent normal on two occasions, and 800 cc, or 20 per cent, on another; in the second patient only one observation was made, the reading of which was 700 cc, or 17 per cent. This last result is of doubtful value, as the patient had fluid in the right thoracic cavity. Both results are very low, but it is felt that the first one is of definite value, for the patient was extremely dyspneic.

A slightly productive cough troubled some of the patients; in a few instances this was a troublesome factor, for with the severe dyspnea and weakness it was very exhausting. Hemoptysis was noted in 2 instances, but was not profuse in either, consisting chiefly of blood-streaked sputum. No infarcts were found in the lungs of these patients, but it is probable that the severe grade of congestion which was found would account for the hemoptysis. The postmortem findings of edema and congestion in the lungs of practically every patient accounts for all the respiratory signs and symptoms mentioned. These findings seem significant, as they show that the first sign of failure of the heart, regardless of whether the injury is on the right or left side of the heart, appears in the pulmonary circulation. In later stages of the disease as the myocardium became weaker, 7 of the patients showed the Cheyne-Stokes type of respiration.

In the group of patients with antecedent heart disease the effect of the infarction was to accentuate those signs and symptoms already present, but they were not altered to any extent and did not change the picture from that ordinarily seen in patients with a rapidly failing heart muscle.

General weakness was present in 15 of the 19 patients, and in some it was so extreme that the slightest movement on their part would cause complete exhaustion. One woman, for instance, by merely lifting an arm would become dyspneic and completely exhausted.

The mental state seems to follow no rule. Patients may remain perfectly rational up to the time of death, though they may seem acutely sick and in a critical condition throughout their illness; while others, whose general condition seems much better in comparison and whose myocardium does not seem to be failing, may be irrational from the beginning. Of the patients studied here

11 were rational up to the time of death while 8 became stuporous, irrational or unconscious.

Almost all of the patients showed distress, anxiety or apprehension in their faces, and the expressions in many were those of extreme suffering. The color of the skin has been commented upon by Libman[22] and others, and in many cases it is certainly striking. In some of our patients the skin was pale, while in others it was a "pasty, ashen color," frequently being cold and moist to the touch, so that the individual resembled a person in "shock." In two of the patients of the group with chronic organic heart disease cyanosis was rather marked, but it was not seen in the others. A diffuse red flushing of the skin was noted in three patients, and, in one instance, this was a striking feature; it was only a temporary phenomenon which appeared twice, lasting about six hours each time. In this patient the skin over the head, body and extremities showed a bright red flush, and during this time she complained of severe heat, and requested that she be fanned or have cold sponges. There was profuse sweating with the flushing but no change in temperature. Profuse sweating without the flushing was also observed in four others soon after the onset. Jaundice was observed in two of the patients.

Loss of appetite, nausea and vomiting were disturbing factors in about one-half of the patients, and in one instance food was vomited which had been eaten the day before. These symptoms and the fact that several of the patients refused to take food for fear of increasing the pain made the problem of nourishment a difficult one. Constipation and diarrhea were infrequent. A very distressing complication was abdominal distention; in some patients this symptom was rather marked and embarrassed an already difficult respiration. In view of these gastrointestinal disturbances during the acute illness it may be significant that seven of the patients had for some months noticed discomfort from gaseous distention after meals, some of them stating that the symptoms were accentuated by the acute illness. The group with antecedent chronic heart disease exhibited none of these features.

Physical Examination. A study of the physical examinations of these patients revealed the fact that there are several signs in this condition which occur with remarkable constancy. The type of dyspnea and the color of the skin are helpful points, but it is from the physical findings in the heart and lungs, together with the history of the illness, that one can expect to recognize the occlusion of a coronary artery with the resulting infarct of the heart.

On auscultation of the lungs, and especially of the bases, one is very apt to hear crackling rales. These persist after deep breath-

[22] Med. Record, New York, 1919, **96**, 521.

ing and coughing and represent the earliest evidence of pulmonary edema, which in turn signifies a failing myocardium. The rales may be confined to the bases or to the regions of the axillæ or again may be widely distributed throughout both lungs. They are usually found soon after the onset of symptoms and were present in two patients who were seen and examined within two or three hours after the beginning of their attacks. In one of these individuals the rales were widely distributed, giving the picture of an extensive pulmonary edema, and with this point in mind it is not unreasonable to believe that many cases of cardiac infarction may be diagnosed as acute pulmonary edema without recognition of the true underlying cardiac condition. The rales were present in 17 of the 19 cases, and, as a rule, persisted throughout the illness, generally increasing as the heart muscle grew weaker. In a few instances, however, they disappeared after a few days. Only one individual in the group without antecedent cardiac symptoms developed a hydrothorax, whereas two of those in the group with antecedent chronic heart disease had a hydrothorax, a third had ascites and all of them had rales widely distributed throughout both lungs. The frequency of the occurrence of rales in the lungs makes it a sign of definite value and especially in those cases resembling acute intra-abdominal conditions, where it may serve as an important differential point and lead to the correct diagnosis.

In the physical examination, when one considers all factors in an effort to determine the condition of the heart, one is able to find many points which individually and collectively lead to one conclusion, namely, a weak heart action. The ease with which dyspnea is provoked, exhaustion from the least effort, a weak and feeble pulse, and then in the heart itself an apex impulse that can neither be seen nor felt and scarcely audible heart sounds, all these findings indicate a failing heart. By percussion the heart was found to be enlarged in fourteen instances; in the other five the hearts, while apparently within normal limits on percussion, were found to be enlarged at necropsy. The enlargements, as a rule, were not great but there were exceptions, as shown by the weights given later. On auscultation one could scarcely hear the heart sounds. Those heard in the apical region are described as "weak," "faint," "distant" and frequently of a "tic tac" quality. The same condition was found to be true in listening over the base of the heart, except in 6 individuals in whom the systolic blood-pressure was elevated and in whom there was an accentuation of the aortic second sound. Of the 15 patients in the group with the acute onset of symptoms, 6 had systolic murmurs which were heard best in the apical region, but it was felt by the observers that these did not indicate valvular lesions except in the 1 patient who had had rheumatic fever. In the group of patients with chronic heart disease all were found to have blowing systolic murmurs

at the apex. Pericardial friction rubs were heard in only 2 patients, and in 1 of these a definite pericarditis was found after death. In 4 other patients necropsy revealed a fibrinous exudate and other signs of a pericarditis, but no friction rubs had been heard in these individuals during life. No signs of pericarditis were found in the patients in the group with chronic heart disease either before or after death. Pericarditis has been claimed by some to be present in all cases of cardiac infarction, but in this series many of the infarcts were deep within the myocardium, and as a result no inflammation of the pericardium resulted. These findings then give to the pericardial friction rub its true value as a diagnostic sign, namely, that if present it is an additional point in favor of infarction, but its absence is of no diagnostic significance.

Pulsus alternans was looked for in only three of the patients and was found in two of them. Likewise a protodiastolic gallop rhythm was noted in six instances. These are signs which are frequently found when sought for, and it is very probable that they occurred in many others of this series.

Examination of the peripheral arteries revealed little that was of value in a diagnostic sense. One expects to find a certain amount of sclerosis in the bloodvessels of patients the age of these, and all of them showed it, while about two-thirds of them had marked sclerosis of the radial, brachial and temporal arteries. The fact that some had only a slight change in the peripheral vessels merely illustrates the fact that the condition of these vessels is no index of the condition of the vessels elsewhere in the body.

Blood-pressure observations showed a wide variation, but the significance of the readings is not great unless the time at which they were made is considered. In several instances only single readings were made upon entrance to the hospital, while in others numerous records were obtained. One patient, for instance, showed many rapid changes of blood-pressure. It happened that she had temporary tachycardia with a rate of 160 beats per minute, and during this time her systolic blood-pressure was so low that a reading was impossible but a few minutes later her rate changed to 60 beats per minute and at the same time her blood-pressure rose to 150 mm. of mercury. Several other patients also showed fluctuations, so that a single observation is of little value.

The abdominal examination is an important one, for it is here that one is most frequently misled in attempting to make a diagnosis. The pain is frequently localized either in the epigastrium or in the right upper quadrant, rarely below the umbilicus. At times there may be spasm of the muscles or the wall of the abdomen with tenderness on pressure, or less frequently a so-called "board-like" belly, so that when the physical examination is limited to this region surgical treatment certainly seems to be indicated.

Levine and Tranter[23] and other writers have emphasized the resemblance of cardiac infarction to acute abdominal conditions. In addition to the findings just mentioned one frequently finds an enlarged, tender liver. This observation was made in about half of our patients and probably represents another sign of a failing circulation.

Laboratory Findings. There are two other signs in cardiac infarction which are almost constant and tend to confuse one with acute inflammatory conditions, especially if the pain is in the abdomen, namely, fever and leukocytosis. Fever is commonly present and in one patient began within twenty-four hours of the onset. The average height of the temperature was 101° or 102° F., though some temperatures ran as high as 104° F. Other patients had subnormal temperatures with a terminal rise to above normal. Levine and Tranter noted a leukocytosis in their 2 cases, but few other authors have noted this fact or realized the importance of this sign. Its real significance is obvious when one notes that only 3 of the 19 patients did not have a leukocytosis. In these 3 only one count was made. The cause of the fever and the leukocytosis without the presence of an infection is not absolutely clear. It is not unreasonable, however, to consider the necrotic heart muscle as a foreign protein which upon being absorbed into the circulating blood produces fever and leukocytosis, as is known to occur when a foreign protein is injected into the blood stream. Furthermore, histologic study of the heart muscle shows many leukocytes in the infarcted area of the heart. These two points are of great value, especially in the patients with precordial type of pain, for in their presence one can rule out an attack of simple angina pectoris.

The urinary findings in our cases were consistent with a generalized arteriosclerosis in which the kidneys shared. The specific gravity readings showed wide variations—from 1.008 to 1.036—and in most instances albumin was found. The sediment contained hyaline and finely granular casts. In only 4 instances were further studies made, and in 2 of these the blood-urea nitrogen was increased, the amounts being 40 mgm. and 90 mgm. per 100 cc of blood. At necropsy the 2 patients with increased blood-urea nitrogen were found to have a chronic nephritis of the arteriosclerotic type. The 2 others studied showed normal function tests and only slight vascular changes were found in the kidneys at the postmortem examination.

Clinical Course. The clinical course of the condition after the infarction of the heart takes place is a stormy one. There is no doubt that death is instantaneous in many cases of coronary thrombosis. Osler saw deaths of this type, and in his Lumleian Lectures gives a vivid graphic picture of them. When one reads almost

[23] Am. Jour. Med. Sci., 1918, **155**, 57.

daily of sudden deaths from "heart failure," "acute indigestion" or "cerebral hemorrhage," one questions if he is not reading of the result of a thrombus in a coronary artery. The typical course of a cerebral hemorrhage in most cases is certainly not so abrupt, "acute indigestion" is meaningless, and what other type of heart failure could one expect to find in an ambulatory person able to be at work? Then a second group is recognized in which the first shock of the obstruction is survived and the patient lives a few hours or a few weeks. Here the pain, dyspnea and other signs may persist, and later the early signs of a break in compensation may develop, or all signs and symptoms may improve, and death, without warning, may occur. One patient, for instance, who had almost recovered from his pain and seemed to be improving, while sitting up in bed gave a sudden gasp and fell over dead. Another was lying quietly in bed having complained of an increase in her precordial pain a short time previously, when she gasped suddenly and stopped breathing. A nurse who was at the bedside at the time was unable to feel any pulse after the gasp, and when the patient was seen by a physician a minute later the heart had stopped beating.

The type of death just described is characteristic of this condition, and in this series thirteen of the patients with the acute type of onset died very suddenly. Here, again, the group with chronic heart disease differs from the others, for only one of the four patients in this group died suddenly while the deaths of the other three were gradual, not unlike that of any patient with a slowly failing heart. With this type of death in mind the records were studied to determine the relation of rupture of the heart to sudden death, but no definite relation was made out, many having died suddenly in whom no rupture was found at necropsy. It was noted also that rupture of the heart does not depend upon the age of the infarct, for in one instance the rupture occurred within eighteen hours after the onset of symptoms while in another the heart ruptured two weeks after the onset.

Not all patients, however, die from infarct in the heart; many survive and may live for months or even years. Dock, Herrick, Osler and others have recognized this fact, and it is on account of this point that the recognition of the disease is important. Herrick has followed patients after recovery in whom the lesions were finally verified at necropsy. At the present time two patients from this hospital are being followed who survived the attack and have been ambulatory for several months. The activities of both patients are greatly limited, the least exertion producing dyspnea, and one of them complains of a persistent dull ache over the precordium which becomes worse on exertion. Previous to the infarction both of them had anginal attacks from which they had

obtained relief by the use of nitroglycerin, but since the occlusion of the coronary artery this drug has no effect upon the pain.

Electrocardiographic Studies. From the clinical observations on our patients it was found that the heart rhythm in 12 of them was regular and remained so throughout their illnesses. The others at some time had an irregular rhythm due, for the most part, to premature beats, but in two instances to heart-block. In only one instance did the auricles fibrillate, and that occurred after digitalis therapy, and was transient. In addition to these routine observations electrocardiographic studies were made upon 10 of the patients, although in most instances only one record was obtained on account of the brief duration of the illness. A summary of the findings in these records is given in Table I, and since few opportunities arise for making electrocardiographic observations on patients with cardiac infarction it seems worth while to review these findings very briefly.

In 6 of the patients the cardiac rhythm was regular, although 1 of this number had complete heart-block at the time records were obtained. Of the individuals with irregular rhythm, in 3 it was due to premature beats, the origin of which was ventricular in 2 instances and auricular in the other. In the remaining 1 the irregularity was due to heart-block with frequent changes in rhythm. As this last patient was studied carefully and frequent electrocardiographic records were obtained (see Fig. 1), it will be of interest, perhaps, to discuss the findings in her case more at length. When the patient was first seen it was noted that the heart rhythm was distinctly irregular, due to very frequent sudden changes in rate, there being three distinct rates of 56, 110 and 160 beats per minute. The rapid changes from one rate to the other were without any special sequence and without any subjective symptoms whatever. Twenty-four hours later, however, this patient began to have frequent fainting spells, and auscultation again showed the three rates with definite pauses at the time of the changes in rhythm. It was also observed that at times during the tachycardia (160) the patient would faint and the rate would then change to 56 per minute. Blood-pressure readings during the tachycardia showed a blood-pressure of 50 mm. of mercury or less, so that accurate reading was impossible; but with the change to the slowest rate (56) the systolic blood-pressure rose to 150 mm. and the diastolic to 105 mm. Electrocardiographic tracings were obtained of the two slower rates, but unfortunately only a pulse tracing was obtained of the rate of 160 per minute. When at the rate of 56 per minute the record showed complete heart-block, and several records of a change from this rate to a normal rhythm at 110 per minute were obtained. On the third day there was a marked lengthening of the *QRS* interval and the

TABLE I.

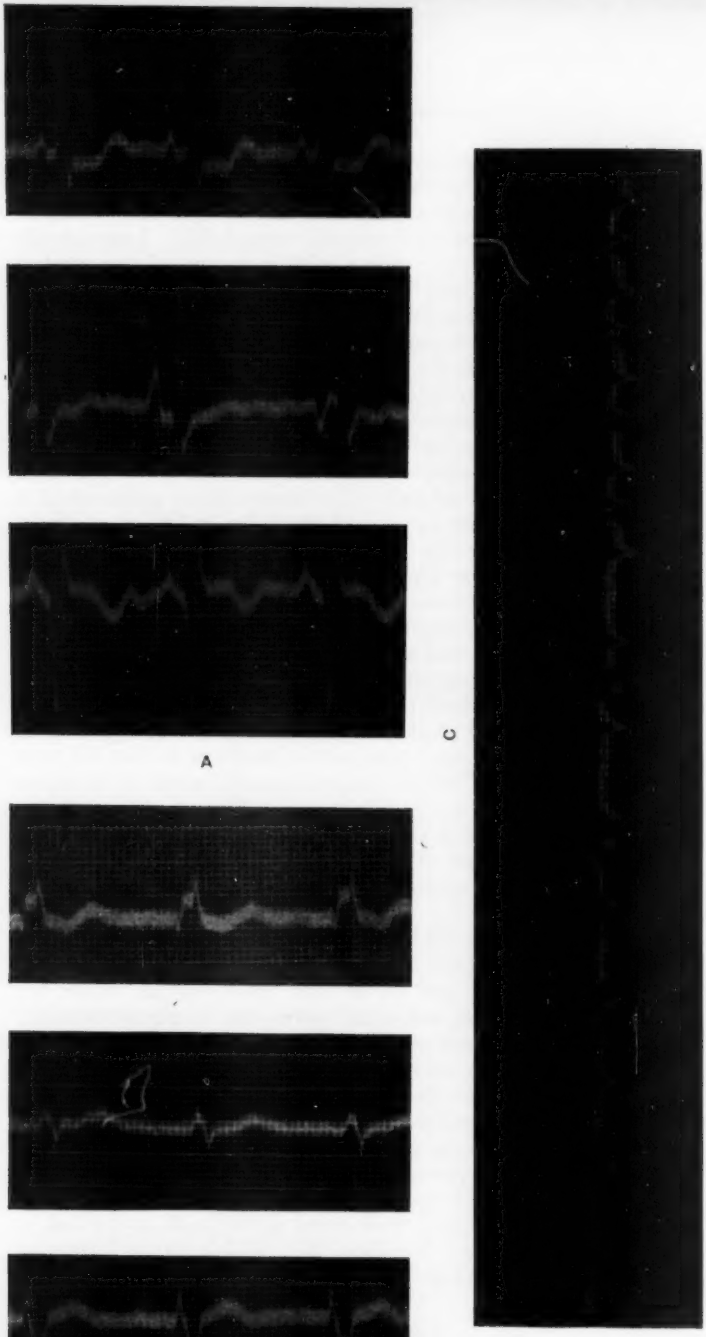
Medical No. and initials.	Rhythm.	Conduction time (P–R interval).	Q.R.S. complex.	Amplitude of of curves.	T-waves.	Time relation of electrocardiographic record to onset and death.	Digitalis.	Miscellaneous.
2741 H. C.	Irregular; premature auricular beats	Normal	Normal	Diminished	Slightly inverted in leads 2 and 3	Record obtained 4 days after onset, 2 days before death	Small amount given.	
3784 J. T.	Regular; complete heart-block	Complete heart-block	Definite spread	Normal	Inverted in lead 1; low but upright in leads 2 and 3	Two days after onset, on day of death	None given	Left ventricular preponderance.
7223 W. S.	Irregular; trigeminy; premature ventricular beats	Normal	Normal	Diminished greatly in all leads	Practically isoelectric in all leads	Nine days after onset, on day of death	Given.	
14600 C. C.	Regular	Normal	Normal	Normal	Isoelectric in leads 1 and 2	14 days after onset 10 days before death	None given before record obtained	
15301 M. H.	Irregular; dropped beats	Delayed and later complete heart-block	Normal on 4th, 12th and 14th days; marked lengthening on 6th and 7th days; typical of intraventricular defective conduction	Normal on 4th, 12th and 14th days; diminished on 6th and 7th days	4th day diaphasic in lead 1, isoelectric in 2, inverted in 3; 7th day diphasic in lead 1; 14th day diphasic in leads 1 and 3; isoelectric in 3	Died on 14th day	Small amount after 1st tracing but not enough to influence the curves; disturbances in rhythm all present before digitalis was given	Dislocation of pacemaker on 13th and 14th days; pulse tracing shows tachycardia of 160 per minute.
14652 A. D.	Regular	Normal	Normal	Slightly diminished	Isoelectric in lead 3	Three days after onset, day before death	None given.	
16216 I. M.	Irregular; rare premature ventricular beat	Normal	Normal	Slightly diminished	Diphasic in lead 3	One day after onset, on day of death	None given	Left ventricular preponderance.
15989 M. N.	Regular	Normal	Normal	Normal	Diphasic in 1; comes off the down stroke of R wave in lead 2; 2d day normal	1st and 2d days after onset; 5th and 6th days before death	After first record	Left ventricular preponderance; second day different form of complex with disturbed pacemaker.
8681 J. J. H.	Irregular; premature ventricular beats	Normal	Normal	Normal	Flat in all leads	Onset indefinite	Given after first record	Left ventricular preponderance.
13063 C. Y.	Regular	Normal	Normal	Normal	Diphasic in 1; inverted in 2 and 3	29 days before death	None given	Left ventricular preponderance; notching of R wave in all leads.

form of the electrocardiogram was entirely different from that of the first day. Again on the fifth day there was delayed auriculoventricular conduction with changes in the rate from 110 per minute to about 55 per minute with complete heart-block. Later records showed a dislocated pacemaker with a return of the electrocardiogram to its original form with a prolonged *QRS* complex. In another patient three distinct rates were noted and records were obtained of the two slower ones; these showed complete heart-block with a rate of 28 per minute and a normal rhythm of about 60 per minute. It seems most probable that the tachycardia in these instances was of the ventricular type, as reported by Herman.[24] The two instances just mentioned are the only ones in which the auriculoventricular conduction time was delayed, for in the other eight patients it was normal. This seems rather remarkable in view of the nature and location of the lesion in the heart, for in many instances there was extensive damage to the septum.

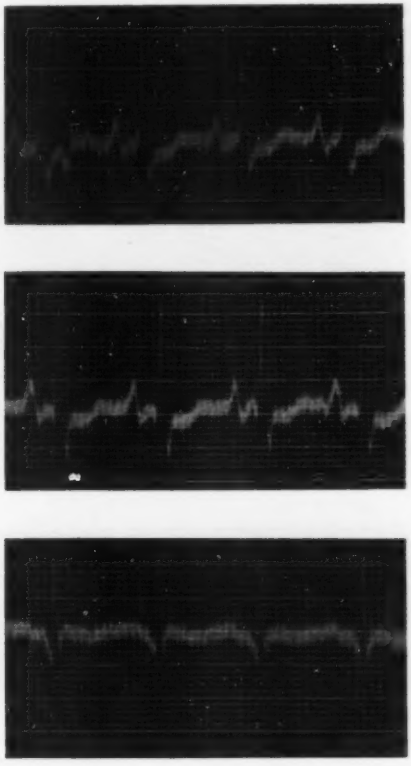
Abnormalities of the *QRS* complex were noted in three of the records, and in each instance there was a lengthening typical of the so-called intraventricular defective conduction. Fortunately several records were obtained upon two of these patients, and it was found that the lengthening of the *QRS* complex was not permanent. In one of them the lengthening occurred on the sixth day after the onset of symptoms of infarction and disappeared on the eighth day. The other patient was irrational, so that the time relation of the date of the electrocardiographic records to the onset of the disease could not be determined. The amplitude of the *QRS* complex or initial ventricular deflection was regarded as diminished in one-half of the patients observed, and in some instances it was so markedly diminished that the curves were almost isoelectric.

It will be seen from Table I that in all of the ten patients there was some alteration of the *T*-waves in at least one of the leads, and frequently in leads I and II, so that these changes, while not abnormal in some of the individual curves, may be significant when taken as a group. Many were inverted while others were isoelectric or diphasic, but in one record only was the *T*-wave found to come off the *R*-wave as described by Pardee.[25] This occurred in lead II, but in a record obtained the next day from this same patient the type of curve had changed, and, along with it, the *T*-wave no longer came from the down stroke of the *R*-wave. The curves of two other patients were practically normal, with the exception of the isoelectric curves which were noted in two leads of one and in the third lead of the other (Fig. 2). A few other incidental findings are noted in Table I.

[24] Jour. Missouri State Med. Assn., 1920, **17**, 406.
[25] Arch. Int. Med., 1920, **26**, 244.


A
B
C

Owing to the variations in the relation of the onset of the attacks to the time that these records were made, and owing to the small number of patients, no definite conclusions can be drawn, but it is obvious that no one form of electrocardiogram is characteristic of this condition. The location of the lesion and the amount of



D

FIG. 1.—Records from Case No. 15301. Frequent changes are shown in the records of the different days. Those of the fourth day are labelled *A*, sixth day *B*, eighth day *C*, and the thirteenth day after the onset or the day of death, *D*. Note the change in the form of the electrocardiogram in *A* and *B* with the return to the original form in *D*. *C* shows the change from a regular rhythm to complete heart-block.

damage to the conduction system probably influence the type of curve, although in this series many of the pathologic lesions appeared almost identical while the curves differed a great deal. Disturbances of the *T*-wave and a diminished amplitude were the most constant findings, but disturbance of the pacemaker, complete

heart-block, delayed auriculoventricular conduction, lengthening of the *QRS* complex and the occurrence of tachycardia and other changes in rate illustrate the great variety of possible alterations in the cardiac mechanism that may be found in patients with cardiac infarction.

Treatment. It seems most probable that the eventual outcome of the individual patient depends upon the amount of damage caused by the infarct in the heart and in the conduction system of the particular patient. Treatment was directed toward absolute

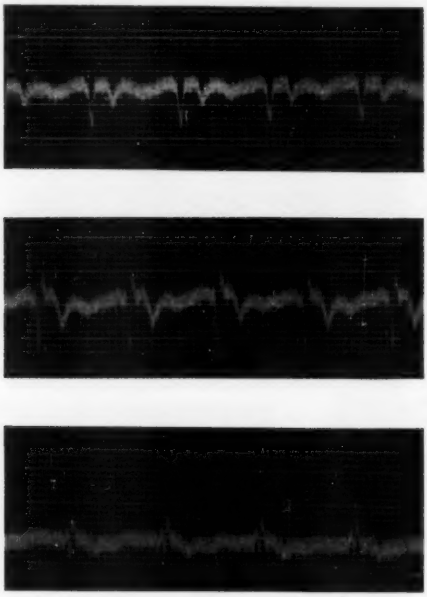


FIG. 2.—Record from Case No. 14652, which shows a practically normal electrocardiogram. This tracing was taken on the third day after the onset of the infarction and on the day before the death of the patient. The interventricular septum was included in the area of infarction in this individual.

rest, and every effort was made to spare the patient any bodily exertion. The fluid intake was limited and in eight of the patients digitalis was employed, the usual result being that the patient felt better and that the circulation improved, as shown by a diuresis and disappearance of the rales in the lungs. These signs of improvement did not occur in every patient who was given digitalis nor can the improvement be credited wholly to this drug; but it was the feeling of the observers that digitalis was beneficial and that it is indicated in this condition. In no instance did the nitrites relieve the severe pain; frequently large doses of morphin were

required and these failed to control the pain in some instances. There were very critical times with some of the patients when the blood-pressure dropped and they showed other signs of collapse, and during these times stimulants were employed freely. Caffein and camphor were used with almost immediate relief, and in one patient who was having frequent changes of heart-rate, with numerous fainting attacks and Cheyne-Stokes respiration, caffein and camphor were used, with the result that the heart-rate became regular in complete block, the blood-pressure rose and the respiration became regular. The effect usually lasted about two hours and was obtained again by repetition of the drugs. No instances of ruptured hearts followed the use of stimulants.

Necropsy Findings An analysis of the postmortem findings in these 19 patients shows several points of interest and explains many of the signs and symptoms observed during life. The one finding which serves as a basis for the whole picture is arteriosclerosis; in practically every one of the patients there was found a generalized sclerosis of the vessels. In some instances the aorta was markedly involved, showing varying grades of the sclerotic process from mere fatty plaques to extensive atheromatous ulcerations with calcification, but in several instances the condition of the aorta was surprisingly good, showing an elasticity normal for the age and with little or no sclerosis, especially in the ascending portion of the arch. These findings in the aorta are interesting because of their relation to Allbutt's views on the cause of anginal pain. In several of the patients with pain resembling the anginal type the pathologist found little in the aorta that would account for it, while in one patient in whom dyspnea was the predominating sign, and there was no pain, the aorta showed an extreme degree of ulceration and even calcification. The degree of sclerosis frequently varied in different groups of vessels, with the exception of the coronary arteries, which in every instance were markedly sclerosed. Their finer branches were frequently closed because of this process and in many of the larger branches the lumen was contracted so that only a very small opening remained. The lack of elasticity of the bloodvessels of the heart could limit the supply of blood to the heart muscle and could most probably account for some of the clinical symptoms.

Rene Marie[26] and Le Count[27] have reported interesting studies of the pathologic findings in the hearts. In view of the finding of enlarged hearts by clinical methods it is of interest to note that the heart was moderately enlarged in practically every one of the 19 cases in our series, varying in weight from 365 gm. to 670 gm., the average weight of fourteen of the hearts being 471 gm., and

[26] L'infarctus du myocarde et ses consequences, Paris, 1897.
[27] Jour. Am. Med. Assn., 1918, **70**, 974.

while the weights of the other five hearts were not given, the pathologist noted the hearts as enlarged in most of those instances. The number showing pericarditis was surprisingly small in view of the nature of the main lesion, but this was most probably due to the position of the infarct and to the fact that many of the patients died before the inflammatory changes became widespread. Only four of the total number showed exudate or injection of the pericardium, a much lower percentage incidence than in the cases reported by Gorham.[28]

The frequence of the occurrence of the thrombus in one particular branch of the coronary arteries was striking. In 16 of the 19 instances the occlusion occurred in the anterior descending branch of the left coronary artery, and in 15 of these the thrombus was situated on the site of a contracture in the lumen due to an atheromatous change in the vessel wall. In one instance the thrombus was not found but the artery was practically closed at one point by an atheromatous constriction of the lumen. As would be expected from the distribution of this branch of the coronary artery the infarction was usually in the anterior wall of the left ventricle. At times the thrombus was so high in the course of the vessel that the interventricular septum and the papillary muscles of the left ventricle were included in the infarction. The posterior descending branch of the left coronary artery was thrombosed in one instance, the infarct being in the posterior wall of the left ventricle. The two other instances in which vessels other than the anterior descending branch of the left coronary artery were involved were in the patients with chronic heart disease. In one the thrombus was found in the descending branch of the right coronary artery, with the infarct in the anterior wall of the right ventricle; in the other the thrombus was located in the posterior circumflex branch of the left coronary with infarction of the posterior wall of the left ventricle. No essential difference was noted in the clinical findings between occlusion of the right and of the left coronary artery. It does not appear, therefore, that a prediction can be made from the clinical findings as to which artery or branch is occluded, but there is a statistical preponderance in favor of the anterior descending branch of the left coronary artery.

Gross examination of the heart outside of the area of the infarct revealed many small fibrous scars. These were verified as such microscopically, and, in addition, many of the small branches of the coronary arteries were found to be closed as a result of an old atheromatous process. In other words, aside from the acute infarction there was, in general, a so-called chronic fibrous myocarditis in a heart with a moderate degree of hypertrophy. In view of these findings it is not surprising that dyspnea occurred

[28] Loc. cit.

when any increased strain was thrown upon the heart, even before the occlusion of the coronary artery. Indeed, it is difficult to understand why these patients did not show more severe signs and symptoms referable to the heart before the onset of the infarction.

FIG. 3.—Acute degeneration of the myocardium in a patient who died about twenty-four hours after the occlusion of the coronary artery. The muscle fibers show swelling, granulation and loss of striations, and there is marked shrinking of the nuclei. (High power.)

Sections through the area of the infarct were practically identical in every case. Acute necrosis with rupture and fragmentation of the muscle fibers was practically always found, except in the patients in whom death resulted almost immediately after the infarction. In these there was a coarse granular appearance within the muscle fibers, the nuclei of these fibers being small and piknotic (Fig. 3). Edema of the heart muscle was also a frequent finding and

a moderate amount of fatty degeneration was present in a few instances.

In later stages or in patients who died weeks after the infarction fibrous changes had begun to appear at the site of the infarct. Following the acute stage of the infarct in a case of coronary thrombosis, repair begins, the area of infarction being replaced by granulation tissue, and, finally, if the patient survives long enough a fibrous cicatrix is formed. Very small scars of this type are frequently found distributed throughout the heart muscle in individuals

FIG. 4.—This section through the area of infarction shows necrosis of the myocardium and the exudate of polymorphonuclear leukocytes. (Low power.)

with marked sclerosis of the coronary vessels, and they are possibly the result of closure from sclerosis of the very small branches of the coronary arteries. When a main branch is obstructed and the patient lives a large fibrous scar is formed; it is possible that these scars may result in the small aneurysms not infrequently found at the apex of the heart. It certainly seems significant that the majority of infarcts occur near the apex in the left venticle and that aneurysms frequently occur at the same point.

Another observation which was made in every case in this series was the presence of polymorphonuclear leukocytes in the infarcted

area (Fig. 4). They were found invading the necrotic tissue and at times in such great numbers that the process resembled an abscess. This probably accounts for the leukocytosis which was found during life. In a few instances there was also a round-cell or lymphocytic infiltration.

With the numerous systolic murmurs heard during life in mind it is interesting to find that in only one instance did the heart show an endocarditis with a valve lesion, and this was in the patient with a history of rheumatic fever. In another instance a very

FIG. 5.—Section of the lung of a patient who died twenty-four hours after the occlusion of the coronary artery, showing the marked pulmonary edema. (Low power.)

small vegetation was found upon the mitral valve, but it was calcified, and in the smears made from it no organisms were found. A frequent occurrence, however, was the formation of numerous small mural thrombi which were generally found over the endocardial surface of the infarcted area.

The interventricular septum was included in the infarcted area a number of times, and, on some occasions, quite extensively. A serial section study of the septum has not been made, but the gross appearance and the amount and extent of the necrosis of the

septum bore no relation to the form of the electrocardiographic curve.

The pathologic changes in the lungs were practically the same in every case. With one exception either edema or congestion was found, and in most cases both were present. This held true for the early as well as the late cases, one patient who died twenty-four hours after the onset of symptoms showing an extensive edema (Fig. 5). This patient was in the hospital at the time the infarction occurred, and although previous to the onset he had not been dyspneic, he became markedly so almost immediately afterward. The heart muscle of this patient is shown in Fig. 3. The degree of edema and congestion varied, of course; in some of the lungs only the bases were edematous while in others the edema and congestion extended throughout. Such an extensive filling of the lungs as is shown in Fig. 5 would readily account for severe dyspnea, a lowered vital capacity and the rales so frequently noted. In several of the patients small amounts of fluid were found in the thoracic cavities, but the quantity was rarely above 200 cc except in the group with antecedent chronic heart disease. In most instances all the abdominal viscera were found to be congested, this being especially true of the liver and spleen. As a result these organs were enlarged to such an extent that the enlargement of the liver was frequently discovered during life. The kidneys were generally congested, and, in addition, the renal vessels were sclerotic. This sclerosis in some instances had reached the stage of a vascular nephritis, a condition discovered in several of the cases during life. Infarcts were also found in the kidney, spleen, lung and brain, but only infrequently.

Briefly the necropsy findings in cases of coronary thrombosis reveal arteriosclerosis, usually generalized, and especially marked in the coronary arteries. Because of this arteriosclerosis a thrombus forms in one or more of the arteries, with a resulting infarct of the heart. Usually the anterior descending branch of the left coronary artery is occluded and the infarct involves the left ventricle and part of the septum. In the necrotic tissue polymorphonuclear leukocytes are found in great numbers. The heart is generally enlarged, and outside of the area of infarction a so-called chronic fibrous myocarditis is usually found. From the cardiac lesion, in turn, result edema and congestion of the lungs and congestion of the abdominal viscera.

Summary. If then the data from the clinical studies of nineteen patients with a diagnosis, confirmed by necropsy, of infarct of the heart be summarized and a typical case be constructed therefrom we will obtain a picture much as follows: We will find a patient, usually a man, possibly less frequently a woman, beyond the age of forty, probably over fifty, complaining of severe pain over the heart or under the lower end of the sternum, or almost as frequently of pain in

the epigastrium. Less frequently the complaint may be of a sudden attack of extreme shortness of breath, persistent and unrelieved by rest. A glance at the patient gives the warning that the nature of the illness is very serious and the condition of the patient correspondingly so. From the presenting signs and symptoms and from the complaint attention is usually directed to the heart and a few questions soon establish the fact the patient had not had the usual forerunners of heart disease, such as rheumatic fever. Furthermore, in view of the severity of the dyspnea and other symptoms referable to the heart, one is surprised to find either little or no evidence of heart disease in the past history. Dyspnea on exertion, such as climbing stairs, may have been noticed for a few months, or some patients may have experienced a few attacks of anginal pain; but the exceptional person only has been incapacitated or prevented from carrying out his daily routine.

The onset of symptoms with the infarction is very sudden and without warning. The patient may have been in good or fairly good health the minute before being seized by an excruciating pain either in the region of the precordium or in the epigastrium, a pain which in most instances radiates into the shoulders and down one or both arms. Unlike anginal attacks, which may have been experienced previously, it persists, and relief at times seems impossible. With the pain may be an extreme type of dyspnea, or, in some instances, the dyspnea may occur alone. The attack may have begun after exertion or, as frequently happens, the individual may have been asleep at the time of the onset. If the patient has experienced attacks of anginal pain or dyspnea previously he needs no one to tell him that this attack is of an entirely different nature; most patients make this observation for themselves. While the pain of angina pectoris lasts minutes the pain of cardiac infarction lasts for hours or days, the same holding true for the shortness of breath. Closely following the pain and dyspnea may be nausea, vomiting, weakness or even collapse, so that the condition may actually resemble shock. In a few patients the heart may have begun to fail before the onset of the infarction, so that they may have been dyspneic, edematous and bedridden. In these people the occlusion of the coronary artery either accentuates the signs and symptoms already present, or, as is possible, the onset of the infarction may be masked by the severity of the previous illness.

When one examines the patient he is impressed by the severity of the symptoms and by the fact that they seem out of all proportion to the physical findings. A careful search, however, is rewarded by finding enough points to enable one to recognize the true condition in the heart. The skin, a pale ashen color, is moist and cold; the expression of anxiety and suffering suggests the severity

of the condition. In the lungs signs of edema, either a few crackling rales at the bases or scattered extensively through both lungs, give the first clue of the failing circulation. Percussion reveals a moderately enlarged heart, and then, on further examination of it, one is struck by its weak action. The apex impulse can neither be seen nor felt, and on auscultation the weak, distant and scarcely audible sounds indicate also the weakness of the heart. Occasionally a pericardial friction rub is heard, and, if present, is an additional point in favor of infarction. Unfortunately a friction rub does not occur very frequently. One may find a regular rhythm or irregularities due to premature beats or less often to heart-block, and not infrequently one finds a tachycardia with a rate as high as 150 per minute. Electrocardiographic tracings may be helpful, but one cannot expect to make a diagnosis from them alone, as there is no typical or characteristic curve in the condition.

On palpation of the abdomen one is apt to find an enlarged liver which may or may not be tender. In patients with the epigastric type of pain, tenderness and even spasm may be found in this region. Finally the presence of a fever and a polymorphonuclear leukocytosis adds to the number of findings which occur with sufficient constancy to make them of definite value in recognizing the condition. A careful search for and consideration of the points which have been mentioned make the diagnosis of cardiac infarction much less difficult and enables one to treat more intelligently those patients who survive the first stage of occlusion of the coronary artery.

The writer wishes to thank Drs. H. A. Christian and S. A. Levine for many helpful criticisms and suggestions during the preparation of this paper.

HEMATEMESIS IN NEPHRITIS.

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The determination of the cause of hematemesis is often a matter of considerable difficulty. This symptom has become almost inseparably associated with peptic ulcer. And yet the number of cases of gastric hemorrhage due to other causes is considerable.

One of these causes is chronic nephritis or its allied states of arteriosclerosis and vascular hypertension. Massive hematemesis in these conditions is comparatively rare. But it occurs often enough to make us bear it in mind when dealing with an obscure case of this dramatic symptom. In this connection I wish to report the following case:

CASE HISTORY. Mrs. M., a white American housewife, aged thirty-one years, was admitted to the medical service of the Postgraduate Hospital on March 20, 1920, complaining of having vomited a "cupful" of blood five hours previously. Her family history is of no interest. She married at seventeen and her husband and two children are in good health. At fourteen she had typhoid fever with complete recovery. Her appendix, both ovaries and uterus were removed when she was twenty-eight. Following the operation she had good health for two years. The morning of the day of her admission to the hospital she had a severe headache and vomited "a cupful" of bright red blood. Further questioning showed that for the past year she had suffered with severe headaches, becoming increasingly severe in the last three months. During the same period her appetite had been poor; she had been troubled with nausea, and frequently vomited small amounts of clear mucus (rarely any food). She had gradually lost weight (twenty pounds) and had become so weak she could no longer do her housework. For several months she had noticed that any unusual exertion caused moderate dyspnea. Urination had averaged six times during the day and two or three times at night for eight months. During the last month she noticed numbness and formication in her hands and legs. There had been no abdominal pain or other symptoms referable to the gastrointestinal tract except the anorexia, nausea and vomiting noted above.

Physical Examination. The patient was a poorly nourished woman in early adult life. Her skin and mucous membranes were rather blanched. Ears, nose, throat and teeth were all negative. There was no general lymphadenopathy. The lungs were clear except for a few fine, moist rales in the left axilla. The apex of the heart was in the fifth left interspace, 11.5 cm. from the midsternal line; the right border at the sternal margin. The second aortic sound was loud and ringing; there were no murmurs; the action was regular and rate 102. The blood-pressure was 194 systolic and 124 diastolic. On admission the abdomen was not examined because of the recent hemorrhage. Later examination showed no tenderness, palpable viscera, masses or free-fluid. There was no edema. The reflexes were normal.

Ophthalmoscopic Examination. Right fundus: Margin of disk completely obliterated; veins dilated; arteries contracted; numerous stellate hemorrhages scattered over the peripapillary area; large whitish spots here and there in equatorial zone. Left fundus: Similar changes though less marked. (Two days after admission.)

Laboratory Findings. Blood count; red blood cells, 3,488,000; white blood cells, 10,600; hemoglobin (Sahli), 60 per cent; differential, 65 per cent polymorphonuclear leukocytes and 35 per cent large and small lymphocytes. Red blood cells showed slight central pallor.

Urine: Specific gravity, 1010 to 1016; persistent faint trace of albumin; no sugar; few hyaline casts.

Gastric analysis (made three weeks after hemorrhage): Fasting contents, 10 cc; faintly greenish fluid; lactic acid, 0; occult blood, 0 (benzidin and guaiac); Boas-Oppler bacilli, 0; free HCl, 10; combined, 12; total acidity, 22. No food remnants.

Ewald test meal: 60 cc yellowish fluid; mucus, +; bile, 0; lactic acid, 0; occult blood, 0 (benzidin); Boas-Oppler bacilli, 0; free HCl, 16; combined, 14; total 30.

Stool: Examination made three weeks after hemorrhage; bile, ++; no ova or parasites; blood, 0 (benzidin and guaiac).

Roentgen-ray report (Dr. W. H. Meyer): Lungs show no pathology; heart shows left-sided enlargement. Gastrointestinal tract: Stomach hypotonic; diminished peristalsis; no defect seen in stomach or duodenum; stomach empty in six hours; examination suggests only gastroenteroptosis.

Blood chemistry: Urea, 11.4 mg. per 100 cc of blood; creatinin, 2.14 mg. per 100 cc of blood; uric acid, 3.5 mg. per 100 cc of blood; sugar, 0.124 per cent; chlorides as NaCl, 0.419 per cent. (Patient had been on low protein diet several days preceding this examination.)

Phenolsulphonephthalein elimination: 130 cc urine with 30.4 per cent in two hours.

Response to nephritic test meal: Total day urine, 794 cc; specific gravity range, 1008 to 1013; total night urine, 1385 cc; specific gravity, 1007; day urine (sodium chloride), 0.36 per cent; total, 2.85 gm.; night urine, 0.16 per cent; total, 5.06 gm.; day urine (nitrogen), 0.21 per cent; total, 1.69 gm.; night urine, 0.097 per cent; total, 1.34 gm.

Progress Notes. During the first twenty-four hours the patient vomited fresh blood, once about four ounces, once about two ounces and once about six ounces. The vomiting ceased after the first twenty-four hours. She was given the routine treatment for hematemesis, followed by salt-poor diet, forced fluids, sodium nitrite, luminal, chloral and rest. She rapidly improved and was discharged on April 3, having only an occasional headache and gaining in weight and strength. Blood-pressure on discharge was 210 systolic and 118 diastolic. She returned to the hospital on July 25, 1920, saying she had been getting worse for the past month, losing weight and strength and suffering with severe headaches. She was quite dyspneic on slight exertion and vomited several times, but no more blood. Physical examination was the same as during her previous stay in the hospital, except that the retinal hemorrhages were more numerous and extensive. Blood-pressure was 250 systolic, blood chemistry showed no essential change, phenolsulphonephthalein excretion was 28 per cent in two hours. After leaving the hospital August 5, 1920, she became gradually

worse and died in uremic coma October 20, 1920. Autopsy was refused.

Discussion. It is difficult to learn the frequency of hematemesis in chronic nephritis, arteriosclerosis or vascular hypertension. However, since Richard Bright gave us his description of the disease that bears his name, there have appeared from time to time scattered through the literature, chiefly in France, reports of gastrointestinal hemorrhages including hematemesis occurring in these diseases. Bright[1] himself, in 1829, spoke of gastric and intestinal hemorrhages in some cases of nephritis, but he saw only a clinical coincidence in the occurrence and did not suspect the relationship that might exist between them. Even before this Latour, in 1815 (quoted by Riesman[15]), described epistaxis and other forms of bleeding in dropsy; and still earlier Morgagni reported the case of a woman with the odor of urine in her breath, who vomited blood and had epistaxis with beneficial results. Later the association of various forms of hemorrhage, including gastrointestinal hemorrhage in nephritis and uremia was noted and reported by a number of observers. Among these were Rayer,[2] Malmsten,[3] Johnson,[4] Treitz,[5] Fournier,[6] Moxon,[7] Bartels,[8] Dodet,[9] Mathieu and Roux,[10] Monpeurt[11] and Lancereaux.[12] Most of these observers described chiefly the intestinal hemorrhages and their lesions which occur more often than those in the stomach.

In a group of 68 cases of uremia collected by Dickinson,[13] however, there were 3 with hematemesis, and Bonifas[14] reported a severe gastric hemorrhage in a case of nephritis, aged thirty years, with recovery. In reviewing the hemorrhagic manifestations occurring in nephritis, Riesman[15] discusses hematemesis among others. He believed that renal disease was a cause of hemorrhagic diathesis, the factors being hypertension, arterial disease and toxemia, and, further, that there was some toxin in the blood acting on the capillary endothelium and impairing the integrity of the blood. Decreton[16] described a case of gastric hemorrhage and tarry stools in a man showing Cheyne-Stokes breathing, uremia and a high blood urea, 79 mg. per 100 cc of blood becoming 11.7 mg. per 100 cc of blood six weeks later. He then discusses the differential diagnosis of gastric carcinoma and ulcer in patients with hematemesis showing evidence of nephritis, arteriosclerosis and hypertension, pointing out the importance of determining the blood urea before deciding. It is very interesting in this connection to note the low figures for blood urea in the case reported by the writer. The blood chemistry was determined in both instances, however, after the patient had been taking a low-protein diet for several days. Uric acid was increased in the writer's case. Crispin,[17] in a general discussion of gastric hemorrhage, mentions nephritis and vascular hypertension as causes and urges a careful search for them in unexplained cases of gastric hemorrhage. He reports a case of hematemesis

in which a gastroenterostomy was done in 1914 for supposed peptic ulcer. Because of repeated gastric hemorrhages the patient was explored at the Mayo Clinic in 1915, but no ulcer was found. He had a blood-pressure of 185 systolic, slight left-sided cardiac hypertrophy, phthalein excretion of 43 per cent and a negative gastrointestinal roentgen-ray, except for a normal functioning gastroenterostomy. Three months after leaving the Mayo Clinic he had another severe gastric hemorrhage and a blood-pressure of 250 systolic.

Pathology. No uniform pathologic findings have been reported by those who have had the opportunity of studying these cases. Monpeurt,[11] reviewing the work previously appearing on the subject, found that nephritis most often gives rise to intestinal ulcerations, and that in the aged gastric ulcerations do not occur without intestinal lesions. Ulcers in the stomach and ileum in uremia were classified as follows by Gandy[18]: (*a*) Hemorrhagic infiltration; (*b*) simple erosion; (*c*) true ulcer. Treitz[5] described uremic lesions in the stomach and intestines as thinning of the mucous membrane, hyperemia and finally ulcerations; while Lancereaux,[12] in a case of gastric hemorrhage in nephritis, was unable to find any gastrointestinal ulceration. Pineau[19] believed that both hematemesis and melena in nephritis are due to increased blood-pressure, increased permeability of the bloodvessels and minor alterations of the mucosa. A man aged thirty-eight years, dying of hematemesis, is reported by Hirschfeld,[20] who showed at autopsy only marked lesions of sclerosis of the gastric arteries, of which one was the seat of a small aneurysmal dilatation. Widal and Boidin[21] described a patient dying in hematemesis and showing no ulcer or cancer. They found only endarteritis of the gastric vessels. In four cases of pronounced hematemesis Fisher[22] found only small white kidneys.

Summary. 1. A case of severe hematemesis is reported due, as far as could be ascertained, to chronic nephritis with hypertension.

2. A review of the literature shows several reports of this rather unusual complication, but gives no uniform conclusions about the cause or pathology of this symptom.

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REVIEWS.

THE DEFECTIVE DELINQUENT AND INSANE. By HENRY A. COTTON, M.D. Pp. 201; 32 illustrations. Trenton, N. J.: Princeton University Press.

THIS remarkable book presents the widely known views of its author on the relation of infection to mental diseases. An illustration of the many reactions which it can rouse is found in its preface where Dr. Meyer regards the book as a stimulant to the production of well-endowed research centers which will afford "a certain surplus of opportunity instead of the deplorable and disgraceful halfway measures with which the study of mental diseases has had to skimp along."

The reader can well become interested in the writer's positive views: "Psychoses arise from a combination of factors, some of which may be absent, but the most constant one is an intracerebral, biochemical, cellular disturbance arising from circulating toxins, originating in chronic focal infections situated anywhere in the body and probably to some extent in disturbances of the endocrine system." This is a proposition that can be studied without prejudice. The chapter about the pathology of the mouth can be left for bacteriologists and dental surgeons to judge, after they have had plenty of time to satisfy themselves by their own work. The general clinical statement, that in the impacted molars and other infected teeth of children lies the explanation for such abnormal characters as the shut-in personality, cannot be controlled so definitely. In fact in the clinical statements and data which the author gives, the most astonishing feature is the number of interpretations that are possible. The following case will serve as an example. A boy, aged nineteen years, in a profound depression, showed by roentgen-ray studies four impacted third molars, a serious gastrointestinal infection and had badly infected tonsils. He was taken home improved, became maniacal and has been confined in various institutions where no attention has been paid to the gastrointestinal tract.

Many clinical cases are given in some detail to show that recovery and improvement have followed surgical and other procedures directed to the detoxication of the patient. The records of other hospitals, where other methods are practised, will show parallels of these individual cases. We quote from a reprint which by chance

was received in the same mail as the author's book: "I recollect one instance of an inmate who had been four years regarded as a hopeless dement, and for whom an early death was anticipated . . . and yet, a twenty-minute interview showed that this man was merely a profoundly timorous psychasthenic, who had completely lost heart, overburdened with the psychologic puzzles he had been endeavoring to solve before his incarceration. He returned to normal life after four months' careful body and mental nursing." The careful physician will want time enough to see the results of any new therapy demonstrated in some cases which he himself knows pretty well. Many physicians have a group of cases in mind who have gone to Trenton and have not apparently been benefited; it is possible that some of these have not submitted to all the procedures which the author thought necessary. Among other unsettled points there is the question of how much psychic effect is produced by the intense enthusiasm and activity which the new patient meets at Trenton, and as the author suggests, a patient must be glad to believe that his trouble is a physical one from which he can be relieved without much effort on his own part.

It is embarrassing to criticise the author's conclusions as to the value of certain detoxicating procedures when one sympathizes with his position on the restraint of patients, with his optimism, his determination to leave no stone unturned to send a patient home well, and the way in which he has brought into his psychopathic wards the atmosphere of the general hospital. One does not need to turn his back upon these good things to urge slowness in accepting a certain technic which deals with very complicated and varying organisms.

We think the author would agree with the following way of stating his position. There are not many persons who acquire mental disease because their ancestors had it, nor are there many, who, hereditarily tainted, are tipped over by the mental distresses they meet. Most psychotics have been riding in flat-bottomed boats, not in canoes, and it has taken an infection from outside to tip them over. Those people who have infections and do not capsize are veritable rafts in their stability. It is a hopeful view, especially since even the canoe may be kept right side up if the essential disturber, infection, be eliminated. We can hope that in time it will turn out to be a correct view. O.

MEDICAL RECORD VISITING LIST, OR PHYSICIANS DIARY. Revised. New York: William Wood & Co., 1922.

THIS annual visiting list is made up for the year 1923 in the usual attractive form. In addition to the spaces for recording professional services there are many tables of drugs, doses, and condensed information of value for quick reference. W.

DISEASES OF THE SKIN. By HENRY H. HAZEN, A.B., M.D., Professor of Dermatology in the Medical Department of Georgetown University. Second edition. Pp. 608; 241 illustrations, including 2 color plates. St. Louis: C. V. Mosby Company, 1922.

THE present volume contains about seventy more pages than the first edition, published seven years ago. The entire work shows signs of careful revision. Changes have been made in classification and several new subdivisions have been formed. There are a number of new illustrations and some of the old ones have been omitted. The technic of superficial roentgentherapy has been brought up to date and a brief consideration of radium and phototherapy added. Almost every chapter has been improved by some addition or suppression. The discussion of the etiology of eczema shows accordance with the modern viewpoint. The author has previously indicated his interest in skin diseases in the negro race and references to this phase of the subject occur more often than in other manuals. His key to diagnosis is rather novel and decidedly practical. In therapy the writer frequently diverges from the worn path, but he is not at all radical. The entire subject is handled in a direct, common-sense manner. Owing to the lack of a confusing variety of treatment for each disease, the book should be especially useful to the student. Briefly, an excellent medium-sized work on dermatology has been improved and modernized. C.

CLINICAL AND OPERATIVE GYNECOLOGY. By J. M. MUNRO KERR, Professor of Obstetrics and Gynecology, Glasgow University (Muirhead Chair); Gynecological Surgeon, Royal Infirmary, Glasgow. Pp. 832; 225 illustrations and colored plates. London: Henry Frowde, Hodder & Stoughton, 1922.

DR. KERR emphasizes the clinical aspects of gynecology in this excellent book, and this attitude toward the clinical side is strengthened by the inclusion in the text of a large number of abridged case histories illustrative of a certain point under discussion. The sections on Anatomy, Nervous Disorders of Women and Venereal Diseases have been ably handled by colleagues. The very sane discussion of the endorine glands is to be commended. Radium does not seem to be regarded in as wide a therapeutic range as in this country, and its possibilities as a cure in cancer are rather questioned. The operative details incident to the surgical side of this specialty are clearly and briefly described, the line drawings of the stages of operations accompanying the text are well executed. The reviewer notes the omission of the consecutive numbering of the illustrations after a certain point, thus rendering correlation

between them and the foregoing text rather difficult. Personal preference or objection to various operative measures are frankly stated. The color plates by Maxwell are unusually good, as indeed are most of the illustrations. Chapter XX gives a *resume* of the conditions in nearby organs which may simulate pelvic disease. There is little to criticize and much to commend in this well-balanced treatise. W.

A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology. By Torald Sollmann, M.D., Professor of Pharmacology and Materia Medica in the School of Medicine of Western Reserve University, Cleveland. Second edition. Pp. 1066. Philadelphia and London: W. B. Saunders Company, 1922.

If a man may be told by the company he keeps, still more should be revealed by the book he writes. The author's comprehensive presentation within the limits of an octavo volume is, we believe, a demonstration of this axiom. Aiming to combine the broad conceptions of a text-book with the mass of minute details of a reference book, he has had to make liberal use of large and small print, side headings, black face, italics, footnotes and similar devices. Although this often entails as many as six forms of type on one page, we feel that the resultant loss of ease and continuity is more than compensated for by the saving of space and reader's time. Appendix A—a tabulation of average doses in four groups according to their practical importance—should be a useful aid to the undergraduate student; while the bibliography of over six thousand titles should be of great value to students of all grades. K.

Protein Therapy and Nonspecific Resistance. By William F. Peterson, M.D., Associate in Pathology, University of Illinois; College of Medicine, Chicago, Ill. With an introduction by Joseph L. Miller, M.D., Professor of Medicine, Rush Medical College, University of Chicago, Chicago, Ill. Pp. 314. New York: The Macmillan Company, 1922.

This book is a pioneer in its field. It is not a text-book or a dogmatic statement of the subject—the time is not yet ripe for that—but a careful compilation, review and analysis of all the evidence that has accumulated in a voluminous literature. The task has been well performed by a man particularly fitted for it by his knowledge of the problems of immunity and by his large clinical experience with protein therapy, a man who combines enthusiasm with a sound and usually conservative judgment.

Beginning with a historical review, the author describes the various nonspecific agents, the typical reactions produced, and the theories hitherto advanced as to the mechanism of the reaction. He next states in a clear and convincing manner his own conception of this mechanism. The second half of the book is taken up with a review and discussion of the clinical results obtained in a variety of diseases. The final chapter deals with indications and contra-indications. While these are frequently alluded to throughout the book, this chapter might have been a trifle fuller, or perhaps more advantageously placed. A full bibliography with over 1200 references is appended. Protein therapy is finding an increasing application in infections. Its field is that of the clinician as well as the immunologist. This book should have and deserves a correspondingly wide appeal. K.

KIRKES'S HANDBOOK OF PHYSIOLOGY. Revised by C. W. GREENE. Tenth American edition. Pp. 820; 524 illustrations. New York: William Wood & Company, 1922.

THIS well-known text-book has been considerably revised for this new edition. It has certain advantages over most of the other text-books for anyone commencing the study of the subject who needs a comprehensive knowledge of the more elementary facts. These advantages depend partly upon the fact that details of histology and of fundamental biochemistry are given as well as the physiologic deductions that can be made from them, and partly because definite statements are made, while less stress is laid on the evidence on which these statements are based.

Such a statement of the main facts of physiology, without dealing too much in theory, should make the book useful for certain types of students, but this method of teaching is doomed to failure unless the facts are absolutely accurate. Unfortunately, this is not the case in this edition, for there appear to be some serious mistakes, presumably misprints, which greatly diminish the value of the book, and some of which the reviewer mentions in a spirit of friendly criticism in the hope that they will be modified.

Thus, in dealing with the gases found in the lungs and tissues, excellent reproductions of some of Barcroft's curves are included; but further on the oxygen tension of the arterial blood is repeatedly given as 29 mm. of mercury, which is entirely inconsistent both with the curves and figures given previously and with our modern knowledge. In the same place wrong figures for the carbon-dioxide tension in expired air are given.

Another part of the book which requires revision in order to make the physiologic basis agree with the clinical findings is that describing the passage of sensory impulses up the spinal cord.

Other criticisms which might be made are that, while in places much of the book has been brought up to date, including even the latest work of Macleod on insulin, in other places old methods are still described, and even at times old conclusions are drawn. On a subject of such importance as hemoglobin estimations it is a pity that neither the Sahli nor the Haldane method, the two most accurate modern clinical methods, are included; and that in a subject so important as heart sounds, graphic records should still be reproduced obtained by Einthoven, using an obsolete method instead of some of the records that have been obtained recently in this country by Wiggers.

If a few of these errors could be corrected, particularly in the misprints of figures dealing with gases, the book would have a real value as an elementary text-book which covered the whole subject very thoroughly. B.

OTO-RHINOLARYNGOLOGY FOR THE STUDENT AND PRACTITIONER. By GEORGE LAURENS, M.D.; authorized English translation of the fourth revised French edition by H. CLAYTON FOX, F.R.C.S. (IRELAND), with a foreword contributed by SIR J. DUNDAS-GRANT, M.A., M.D., F.R.C.S. Second English edition. 589 illustrations. New York: William Wood & Company, 1922.

THIS translation of the fourth French edition of George Laurens' treatise on diseases of the nose, throat and ear is of special value to the student and general practitioner. The author has endeavored to give to the general practitioner the necessary data which would enable him to diagnose and treat the more common ailments of the nose, throat and ear, making it clear, however, that certain diseases cannot be successfully handled, except by a specialist. Methods of treatment and the more simple operations are described in sufficient detail to enable the general practitioner, with a certain amount of practice to take care of the common diseases. Operations and other technics demanding special training are only mentioned and not described in detail, as the author rightly believes such cases should be referred to a specialist. One of the valuable parts of the book is contained in the "What to Avoid" remarks. Though in a few details we cannot agree with the author, on the whole, the book is a very reliable one and a safe guide for those beginning the study of otolaryngology. It is well illustrated with numerous and clear, though not elaborate, illustrations, and the text is very easily readable. In this edition particular mention has been made of Vincent's angina, hay-fever, rhinometry, pseudo-hemoptysis of laryngeal origin and vaccine therapy. Also aural vertigo and the intratracheal injections of medicated liquids is given special attention. W.

THE ORIGIN AND EVOLUTION OF THE HUMAN DENTITION. By WILLIAM K. GREGORY, PH.D., Associate Professor of Vertebrate Paleontology, Columbia University; Curator of the Department of Comparative Anatomy, American Museum of Natural History, New York. Pp. 548; 353 illustrations. Baltimore: Williams & Wilkins Company, 1922.

IN this very exhaustive treatise is traced the gradual development of the teeth from the earliest times and from the lowest vertebrates up to those of modern man. A detailed review could only be undertaken by a paleontologist. Those seeking the reasons for the present formation of the human dental organs will find here many points elucidated. It is through the labors of such purely scientific workers as the author, that true principles for the modern practice of medicine and dentistry are established. I.

DISEASES OF THE SKIN AND THE ERUPTIVE FEVERS. By JAY F. SCHAMBERG, A.B., M.D., Professor of Dermatology and Syphilis, Graduate School of Medicine, University of Pennsylvania; Dermatologist to the Philadelphia General Hospital and the Jewish Hospital; Fellow of the College of Physicians of Philadelphia; ex-President of the American Dermatological Association. Fourth edition. Pp 625; 228 illustrations. Philadelphia and London: W. B. Saunders Company, 1922.

THE author's excellent book on *Diseases of the Skin* has forty-one additional pages more than in the last edition. The volume has been brought up to date by the following additions: Eczematoid Ringworm or Tinea of the Extremities; Copra Itch; Larva Migrans; Brown-tail Moth Dermatitis; Trichoptilosis; Granuloma Annulare; Purpura Annularis Telangiectodes; Sarcoid; Gangosa; Espundia; Paraffinoma; Leukemia Cutis.

The chapter on Roentgen-ray Therapy has been rewritten, giving the MacKee-unit method for the treatment of various cutaneous diseases. Syphilis has been much amplified, as the third edition of this book contained but twenty-five pages, and in the present volume this subject is covered in fifty-four pages. New pictures have been added under the following headings: Eczema, Pemphigus Vegetans, Herpes Zoster, Lichen Planus, Acne Necrotica, Pityriasis Rosea, Larva Migrans, Xeroderma Pigmentosum, Sarcoid, Syphilis, Yaws, Gangosa, Espundia (Leishmaniasis).

The volume is extremely readable and well edited. K.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Prevention of Goiter.—McClenden (*Science*, 1922, **56**, 269) emphasizes that the goiter belt seems to be a low iodide belt. Practically all the world's supply of iodin is now in the sea, where there is a calculated total of sixty billion metric tons. The writer, therefore, suggests the prevention of goiter by the use of table salt, made from sea-water. A less attractive possibility is the addition of powdered kelp for food.

Arteriosclerosis and Diet.—Newburgh and Clarkson (*Jour. Am. Med. Assn.*, 1922, **79**, 1106) studied the bloodvessels of rabbits, which had been fed on diets containing various percentages of protein. Diets containing 27 and 36 per cent of protein were followed by internal changes which resembled true arteriosclerosis. Large groups of rabbits fed on normal vegetable diets failed to show such changes. The time of appearance and the severity of the vascular change were roughly proportional to the amount of protein fed and the duration of the feeding. All rabbits who ate high protein diets for six months or more showed extensive changes. It is not claimed that human arteriosclerosis is caused by a high protein diet. It is pointed out, however, that carnivorous animals show a higher incidence of arterial disease than do herbivorous.

Phthisiogenesis and Latent Tuberculous Infection.—Opie (*Am. Rev. Tubere.*, 1922, **6**, 525) states that pulmonary tuberculosis in early childhood is not selective; it affects any portion of the lung. It is progressive with almost no tendency to heal or to form fibrous tissue. The miliary form is common; 16 per cent of fatal cases die of men-

ingitis. The incidence of pulmonary tuberculosis at autopsy on children (dead of other cause) agrees substantially with the incidence of infection as indicated by the von Pirquet skin test. Children sick with "masked" tuberculosis—"frequent coughs and colds, attacks of unexplained fever, loss of weight, anorexia and asthenia"—show a very high percentage of positive skin tests and complement-fixation tests. An absolute differentiation between latent tuberculous infection and clinical tuberculosis in children cannot be made. Primary intestinal tuberculosis is well recognized, but the bacillus leaves local lesions along its path of entry in Peyer's patches, mesenteric nodes, cervical nodes, etc. After the seventh or eighth year of life, lung lesion tends to become localized at the apex and the lesion is more fibrotic and more chronic, and is without the caseation of the bronchial lymph nodes, which is common in children. This type of lesion—latent apical infection—is easily differentiated from phthisis (chronic, fibrotic tuberculosis) and is "transformed into phthisis only when the tuberculous lesion becomes active and progressive." At autopsy this type of latent lesion occurs in one-sixth of the people dying from whatever cause. Adult phthisis may be and probably is occasionally acquired in childhood, as is strenuously maintained by von Behring, but by far the most of the children infected under one year of age soon die. The lesion in chronic lung tuberculosis is predominantly fibrotic rather than caseous or pneumonic, and it is probable that the ordinary case is one which has been infected, probably repeatedly, prior to the development of clinical phthisis. Many workers have reported fibrotic lesions (phthisis-like) in experimental animals which have been reinfected, but not in animals with primary infection. The primary infection in animals has more the appearance of the tuberculosis of infants and young children. Adults may become repeatedly infected, even though sources of infection are at times difficult or impossible to find. Most adult tuberculosis comes at a period when the childhood infections are healed. In adults the course is chronic and the disease fibrotic because the adult has a relative immunity from a former infection. Adult phthisis seems to come usually from infection through the air passages. The extensive experiments of Calmette do not convince one that phthisis necessarily arises from infection through the intestinal tract. It has been found that from 350 to more than 500 times the number of tubercle bacilli are required for infecting an animal by ingestion as by inhalation. Sputum from phthisis remains a great source of danger, as does also contaminated milk.

Pernicious Anemia and Protein Sensitization.—FABER (*La presse méd.*, 1922, **81**, 873) for several years had good results in the treatment of pernicious anemia from the administration of fermented milk (kefir). It was thought that the action of this kefir might be due to its protein effect. Therefore a case of pernicious anemia which failed to respond to the ordinary methods of treatment was when almost moribund given an intramuscular injection of 5 cc of sterilized milk. There was an intense immediate reaction with a high fever, which was followed shortly by a very marked subjective and objective improvement. Subsequent cases similarly treated have shown various results but some have been definitely improved. These observations led Faber to some

very interesting speculations concerning the pathogenesis of pernicious anemia. He summarizes the familiar arguments for the origin of pernicious anemia in an intestinal intoxication. He points out that the achylia, which is known frequently to precede the onset of the anemia, will permit an abnormally abundant bacterial flora in the part of the intestine in which absorption is most rapid and will also permit the proteins of the food to reach the small intestine practically unchanged. Thus he thinks proteins may be absorbed as such and sensitization result. He suggests then that pernicious anemia may be a "sort of chronic alimentary anaphylaxis" and that the relapses and remissions may be due to variations in the immunity of the organism.

Reticulated Erythrocytes.—KRUMBHAAR (*Jour. Lab. and Clin. Med.*, 1922, **8**, 11) suggests the word "Reticulocyte" to designate red blood cells revealing a reticulum by methods of vital staining and that when the normal percentage of those cells in the peripheral blood is exceeded the condition be designated "Reticulosis." He reports that in experimental plethora in dogs the reticulated cells are greatly diminished. The normal variation in reticulated cells in the human adult is from 0.1 to 1 per cent. Infants show an increased percentage during the first week of life. By the end of the first week the picture should resemble that of the adult. It is pointed out that the degree of reticulosis is a better index of the functional activity of the bone marrow than the study of polychromatophilia or nucleated forms.

Erythropoietic Action of Germanium Dioxide.—KAST, CROLL and SCHMITZ (*Jour. Lab. and Clin. Med.*, 1922, **7**, 643) treated 16 cases of anemia with germanium dioxide. They gave 100 to 200 mg. daily or every two or three days until about 1 gm. had been given. An apparent erythropoietic action was observed in several of these cases. The most marked changes in red count and hemoglobin occurred in anemia secondary to hemorrhage. Total solids in the blood were increased, but not sufficiently to explain the increase in red cells on the ground of decrease in plasma volume. No deleterious effects of the drug were noted.

Intravitam Bone Marrow Studies.—MORRIS and FALCONER (*Arch. Int. Med.*, 1922, **30**, 485) have devised a drill for trephining long bones to secure living bone marrow for histological and cultural study. They have obtained marrow specimens from numerous animals without untoward results. The marrow obtained by this method showed the same characteristics as were visible in sections of the marrow made after killing the animal. The authors feel that this method of examination can be used safely in human beings and that it might throw much light on early phases of obscure blood diseases.

Etiology of Scarlet Fever.—BLISS (*Jour. Exper. Med.*, 1922, **36**, 575) reports further studies of scarlet fever strains of streptococcus. Contrary to the traditional idea that this organism is present in many but not in all cases of scarlet fever, Bliss reports its occurrence in 100 per cent of scarlatina patients during the first week of the disease. While these organisms had no special morphological or cultural criteria,

and in fact varied in their growth characteristics, 80 per cent of them were identical as regards their reaction to specific agglutinating sera. Of special interest was a strain recovered from a mastoid infection with a scarlet rash, which serologically fell into the scarlatinal group of strains. The writer is very conservative in interpreting his findings, but implies that a special group of hemolytic streptococci is at least an invariable concomitant of scarlet fever.

Thyroid Function. — MARINE (*Phys. Reviews*, 1922, **2**) reviews our present knowledge of the functions of the thyroid gland. He points out that the thyroid has been shown to develop from a single ventral tubular down-growth of pharyngeal endoderm. The so-called "lateral thyroid anlagen," formerly believed to form the lateral thyroid lobes, are accidental inclusions which later undergo atrophy. A review of the literature shows that the relation between the number of mitochondrial granules and the pharmacological activity of the gland is not generally accepted in view of the abundance of these granules in the thyroid in myxedema. Thyroid adenomata are believed to develop from cell rests which atrophy under normal conditions but which form adenomata under certain conditions calling for increased thyroid activity. Thyroidectomy in animals has resulted in an average maximum reduction in total metabolism of 35 to 40 per cent, which figure "corresponds closely to that observed in the severest forms of human cretinism and myxedema and may be designated as the myxedema level." A close interrelationship of suprarenal cortex and thyroid has been observed, and Marine believes that exophthalmic goiter is intimately involved with cortical exhaustion and epinephrin stimulation. The review includes a survey of our present knowledge of the bearing of iodine metabolism upon the physiology of the thyroid gland and of the interrelationship of the thyroid and the other glands of internal secretion. The paper is brief and the clinician will find it well worth the reading in detail.

THERAPEUTICS

UNDER THE CHARGE OF

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Report on Artificial Pneumothorax.—BURRELL and MACNALTY (*Medical Research Council*. Special Report No. 67, abstracted as one of the leading articles in the *British Medical Journal*, September 30, 1922, p. 606) in the first part of the report discuss pneumothorax from all

aspects and give a summary of Burrell's first 150 cases. It is found that patients with a low resistance and in whom the disease is progressing rapidly are but little benefited by the operation; patients with high power of resistance usually do well with sanitorium or other medical treatment. It is in the intermediate cases (those in whom the disease is subacute and in whom the healthier lung is not too seriously involved) that artificial pneumothorax offers the greatest hope of permanent benefit. The risks of the operation are so slight and the danger of the disease spreading so great, that all patients of this class are entitled to the probable benefit afforded by the operation. Burrell's 150 cases may be divided into three classes: in the first group, an efficient pneumothorax was produced; in the second, only a partial pneumothorax was induced and in the third, none was obtained because of the pleural adhesions. There were 107 cases in the first group; in 40 the disease was arrested and in 22 there was improvement. The result in the other groups was not nearly so good. The second part of the report consists of the answers to a questionnaire sent to sixteen British physicians. The replies indicate that these physicians are unanimous in their approval of pneumothorax as a therapeutic measure, and their approval gains weight when it is learned that these sixteen physicians have induced pneumothorax in 14,000 to 15,000 patients. There is a difference of opinion as to which patients are most suited for the collapse treatment; but the general consensus of opinion appears to be that after institutional treatment has been given a fair trial, as soon as it is noted that the disease is not responding, pneumothorax should be induced. The collapse treatment shows that the first essential to the arrest of active pulmonary tuberculosis is immobilization and the more complete the rest given the tuberculous lung, the better the healing. Thus the same principle is applicable to surgical and pulmonary tuberculosis, and that is, rest.

The Intratracheal Injection of Oils for Diagnostic and Therapeutic Purposes.—CORPER and FREED (*Jour. Am. Med. Assn.*, 1922, **79**, 1739) studied the effects produced by the intratracheal injection of small quantities (0.05 to 1 cc) of some oils that have been highly recommended in the treatment of tuberculosis. Some of these substances have hitherto been regarded as quite harmless to the pulmonary tissue and of considerable bactericidal power; others were thought to be sufficiently irritant to elicit a mild fibrosis which promoted the healing of the diseased area (lung abscess, bronchiectasis, etc.). Corper and Freed found that the injection of so-called "bland" oils is accompanied by grave danger. Chaulmoogra oil and the mixed esters of chaulmoogra oil are, when injected into rabbits, intensely irritant and cause profound pathological changes in the lung which may range from acute pneumonic consolidation with abscess formation to a proliferative bronchopneumonia, depending on the localization of these oils in the lung and on their concentration. Even so dilute a solution as 10 per cent chaulmoogra oil in olive oil or liquid petrolatum produces a distinct proliferative bronchopneumonia. Olive oil or liquid petrolatum injected intratracheally is aspirated into the pulmonary alveoli and may remain there unabsorbed for months causing a mild type of localized pneu-

monia. It is probable that the local application of one of these oils to the larynx or to a bronchus through the use of the bronchoscope, is followed by the aspiration of the oil from the site of application and by its distribution throughout the adjacent alveoli. The conclusion that seems obvious is that even "inert" oils are dangerous when aspirated, and that the greatest care must be used in introducing any foreign body into the normal or diseased lung.

Temporary Disturbances of the Circulation and Respiration Due to Local Anesthetics.—The object of the studies reported by Ross (*Jour. Lab. and Clin. Med.*, 1922, **8**, 1) was the determination of the changes occurring in the respiratory and circulatory systems when the commonly used local anesthetics were applied to animals by the same methods that are used in medical practice. The local anesthestics (cocain and procain) were injected into the tonsillar tissue or painted on the pharynx; the epinephrin was injected submucously into the tonsils. The submucous injection of epinephrin (adrenalin) elicited practically no effects, raising blood-pressure only 8 per cent and accelerating breathing by 16 per cent. Cocain injections had a more marked effect, elevating arterial blood-pressure by 83 per cent and venous pressure by 100 per cent; the heart rate was increased only 3 per cent and respiration 9 per cent. When both epinephrin and cocain were injected into the same tonsil, profound circulatory and respiratory changes ensued; arterial pressure rose 233 per cent, and venous pressure 467 per cent; the heart rate declined 18 per cent and respiratory rate was doubled. The preliminary injection of atropin and morphin lessened these striking changes to a slight degree only. In another series of experiments cocain (20 per cent) was painted on the pharynx and subsequently epinephrin was injected into the tonsils. The effects on circulation and respiration were greater than when epinephrin alone was injected but much less than when both the epinephrin and cocain were injected together. Procain (20 per cent) when swabbed on the tonsils and pharynx caused no definite reduction in the effects of cocain-epinephrin injection. Ross draws the following conclusions: The submucous injection of epinephrin and cocain into the tonsillar tissue brings on systemic reactions similar to those that follow the intravenous injection of these drugs, and causes an enormous increase in arterial and venous pressures. The latter is increased more than twice as much as the former, and the great rise in venous pressure may cause cerebral asphyxia and thus explain all the temporary disturbances that occur in medical practice after the use of local anesthetics. Cocain and epinephrin injected submucously are powerful synergists. Sufficient cocain is absorbed from sponging the pharynx with a 20 per cent solution to increase markedly the sensitiveness to epinephrin. Novocain and epinephrin are not synergists and novocain does not materially neutralize the extent of the synergistic action of cocain and epinephrin.

PEDIATRICS

UNDER THE CHARGE OF

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The Rate of Secretion of Breast Milk.—SMITH and MERRITT (*Am. Jour. Dis. Children*, 1922, **24**, 413) from their observations noted that nursing infants obtain the greater part of their feeding of breast milk in the first few minutes, from 40 to 60 per cent in the first two minutes and from 60 to 85 per cent in the first four minutes. This holds true whether the supply is abundant, moderate or scanty. After eight minutes very few babies get any milk whatever. Only 17 of their observations showed any increase in weight after eight minutes. Fourteen of these were from good feedings and only 3 of them obtained milk after ten minutes. A few large vigorous infants nursing from an abundant supply, may get small amounts of milk up to sixteen minutes. The babies who needed both breasts usually got less from the second breast than from the first, except where one breast regularly yielded a better supply. The rate at which a baby gets milk from the second breast is similar to that of the first breast. After that time very little is obtained. The time after which a baby gets no more milk from the second breast is usually shorter than on the first breast. The poor feedings are usually completed in a shorter time than the good ones. When the breast supply is evidently failing, the baby gets all that he will get in from three to five minutes as a rule. It does no good to leave a baby a longer time at breast in hopes that by so doing an additional amount will be ingested. If a baby empties the breast in from five to eight minutes and shows no evidence of discomfort from an adequate feeding obtained in that time, there seems to be no good reason why he should not take his bottle in the same time. If the nipple holes are of good size so that the milk flows freely, nearly all strong infants will finish the bottle in less than ten minutes. They evidence less distress than the nurse does over the rapid feeding. On the other hand a slow nipple either discourages the infant so that he will give up in disgust before he has finished, or else make him swallow so much air that he vomits or has colic.

Faulty Diet and Its Relation to the Structure of Bone.—SHIPLEY (*Jour. Am. Med. Assn.*, 1922, **79**, 1563) says that there are several dietetic principles concerned in the growth of bone. First there is an uncharacterized organic substance which is distinct from fat soluble A. This is found in certain oils principally those of the cod, burbot and shark livers in large amounts. It is present in very small quantities in butter fat and in cocoanut oil. Fat soluble A is missing from the latter of the[se] It may belong to the group of the vitamins, and is known to be much more resistant to heat and oxidation than fat soluble A. Other

essential principles are calcium, phosphorus, water soluble B and fat soluble A. Water soluble C was found to influence the structure of the bone of the guinea-pig, but the rat either does not need this substance or is able to synthesize it. The writer was able to show that the lack of fat soluble A was not responsible for the developing of rickets. Bones of animals whose diet is adequate except for fat soluble A are perfectly calcified, but a high degree of osteoporosis develops. The same result follows the administration of diets having a deficiency only in water soluble B. When this factor is deficient there is also an aplasia of the marrow, such as follows complete starvation, and later there is hemorrhage into the medullary cavity. If a guinea-pig is deprived of water soluble C, his bones are identical with those of a rat which has been given an insufficient supply of water soluble B. When the organic factor mentioned before is absent from the diet or only present in small quantities, all other factors being so far as can be ascertained in optimal concentration, any variation in the ratio between calcium and phosphorus results in a profound disturbance in the structure and functional capacity of the skeleton. A disease of the osseous system which has the clinical and pathological characteristics of rickets may be induced in rats by diet. It may be induced by diets which are within certain limits low either in phosphorus or in calcium, all other dietary factors being maintained at the optimal level for growth and function. If the organic factor which is so abundantly present in fish oils is supplied freely, rickets will not develop in spite of a faulty ratio of calcium to phosphorus in the food. Cod-liver oil will protect against rickets, or cause the healing of the lesion even if the salt content of the diet is such that rickets will invariably develop without the oil. It was found that animals were enabled to compensate for faulty calcium-phosphorus ratiosin the diet if they were exposed to the rays of the sun or to the iron-chromium or cadmium arcs or to the light of the mercury vapor quartz lamp. The same changes are induced under the influence of the rays as by cod-liver oil.

Immunization Against Measles.—HERMANN (*Arch. Pediat.*, 1922, **39**, 607) claims that 75 per cent of the deaths from measles occur in infants under two years of age, and 90 per cent under five years. He feels that any method of immunization which aims to control or eradicate this disease must be employed in early infancy on all or nearly all children. Infants, whose mothers have had measles are relatively immune during the first five months of life. This immunity gradually disappears, but in many it persists to the sixth or eighth month. The immune bodies in the mother's blood are probably conveyed to the fetus through the placental circulation. Artificially fed, as well as breast fed babies enjoy this relative immunity. It is not conveyed to any great extent through the breast milk, for infants of six or more months, who are still nursed are just as susceptible as bottle fed babies. In measles the infectious material is regularly present in an active form in the nasal discharge from twenty-four to forty-eight hours before the eruption begins. It is not necessary to isolate and identify the infectious material, or to obtain its growth in pure culture, in order to immunize against the infection. In measles the infectious material is conveyed

usually from the nasal mucous membrane of the patient to the nasal mucous membrane of the child infected. Immunization follows the same path. The nasal mucous discharge of patients, free from other diseases, is taken from twenty-four to forty-eight hours before the appearance of the eruption. It is mixed with a small amount of normal saline solution, and bacteria and other extraneous material separated by centrifugalization. If passed through a Berkfeld filter, the organisms are eliminated but the virus loses some of its potency and cannot be depended upon for the purpose of immunization. A little tricresol is added as a preservative. A few drops of this solution is applied to the nasal mucous membrane of the child to be immunized. Only healthy infants between four and five months are immunized. The method attempts to convert the temporary relative immunity into an immunity which persists during the first few years when the disease is the most dangerous. The best results are obtained in those cases in which a rise in temperature follows on the eighth to the sixteenth day.

Congenital Hypertrophic Pyloric Stenosis and Its Treatment by Atropin.—Haas (*Jour. Am. Med. Assn.*, 1922, **79**, 1314) says that uncertainty of etiology is the cause of the differences of opinion in treatment. Medical treatment was formerly practised until the Rammstedt operation caused surgery to be advocated exclusively. To see and to feel a pyloric tumor, he thinks, and to observe the histologic appearance makes faith in any other view difficult. He thinks, nevertheless, that the problem is a medical one, and that atropin is practically a specific. He holds that pyloric stenosis is only an advanced degree of pylorospasm. It is only a single manifestation of a general hypertonic state, whose etiologic factor is an overaction of the vagus portion of the autonomic nervous system. There is usually an excitability of severe degree of all motor functions. This condition has been described variously as the hypertonic infant, myotonia, myotonia spastica perstans, arthrogryposis, essential contractures, pseudotetanus, tetanoid conditions, infantile tetany, spasmophilia and vagotonia. Experimental work supports this view. Further support is found in the reports of cure by other than surgical methods. Differential diagnosis between pylorospasm and pyloric stenosis is practically impossible. The symptoms of pyloric stenosis are projectile vomiting, visible peristalsis, constipation, starvation stools, rapid loss of weight and pyloric tumor. Closer observation will reveal pallor, lividity, loss of turgor, circumoral cyanosis, cold, clammy, cyanotic hands and feet, subnormal temperature unless obscured by starvation elevation, and spasm not only of the pylorus but often of the larynx, pharynx, esophagus, cardia and various portions of the intestines. There is also hypertonicity of the skeletal muscles. Irritation of the infant nervous system produces an effect predominantly stimulating. An inhibiting effect is virtually absent. In the treatment certain points should be observed. Errors in diet or hygiene must be corrected. In advanced cases saline must be given subcutaneously at frequent intervals, until enough fluid is taken by mouth to supply body needs. Atropin, like digitalis, must be active. In the milder cases the drug may be given by mouth or in

the bottle, and in breast-fed babies in a teaspoonful of water, before feeding. In the severe cases the drug must be administered hypodermically until vomiting is controlled. The dose is variable, from $\frac{1}{1000}$ grain at each feeding up to a maximum which either controls symptoms or produces physiologic reaction. Treatment may be required only for a few weeks or it may be necessary for the most of the first year. Few cases require a smaller dose to begin with. Occasionally constipation with severe tenesmus occurs. This is relieved by the omission of a few doses of atropin. The author bases this report upon more than forty cases.

Toxin-antitoxin Immunization Against Diphtheria.—PARK (*Jour. Am. Med. Assn.*, 1922, **79**, 1584) has had twenty-five years of experimental and practical experience in the immunizing effect of toxin-antitoxin injections, and has made many Schick tests. He has found that three injections of a suitable toxin-antitoxin, 1 cc each, at intervals of one or two weeks, will cause about 85 per cent of susceptible children or older persons to develop sufficient antitoxin to give the negative Schick reaction and produce marked if not absolute protection against diphtheria. The development of the immunity is slow. The amount of antitoxin sufficient to prevent the positive Schick reaction develops in the different children in from one to six months after receiving the injections. Antitoxin as heretofore must continue to be used to produce immunity immediately. The duration of the immunity in at least 90 per cent of the children is for more than six years and probably for the remainder of life. There seems to be no difference between these and those who develop antitoxin naturally. Toxin-antitoxin injections should not be given without an interval of two weeks having elapsed since the administration of antitoxin. Otherwise the toxin is slightly overneutralized and the resulting development of antitoxin is lessened. Mixtures made from old toxin and antitoxin are fairly stable and may be used for a period of one year. Even such preparations are at their best when first sent out, as the mixtures slowly tend to become at first neutralized and then slightly antitoxic. This change gradually lessens the immunizing power of the toxin. The toxin-antitoxin should be kept cool and in a dark place. It is best to use the mixtures within three months of final preparation. A toxin-antitoxin mixture of stabilized materials which is safe when it leaves the laboratory cannot become toxic on being kept. The Schick test is an extremely reliable means of separating the individuals who have antitoxic immunity from those that have none. Although it is a simple test, it must be carried out with extreme care. The toxin must be retained intracutaneously, and the toxin must be neither 25 per cent more or less than the desired amount. It is extremely important to choose a glass of suitable chemical composition for the containers in which the toxin is to be placed, as rapid deterioration may ensue from improper containers. The preliminary Schick test is usually omitted in children under three years of age. Two-thirds of these require the toxin-antitoxin anyway. It is not certain that those who give negative reactions are immune. In school work the Schick test is usually omitted up to the sixth year,

because it is easier to inject the children than to wait for the test. After the sixth year the preliminary Schick test should be made whenever possible. No child should be pronounced immune upon receiving three injections of toxin-antitoxin. A negative Schick test is absolutely necessary before one can be certain. The toxin-antitoxin injections are inadvisable before six months of age. During this time most infants retain the antitoxin received from their mothers. Up to the age of three months immunizing injections are usually ineffective. During the first three years there is almost no annoyance from the injections.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Agglutination of Red Blood Cells by Arsphenamin.—OLIVER, DOUGLASS and YAMADA (*Jour. Pharm. and Exper. Therap.*, 1922, **19**, 187, 199 and 393) have been conducting important studies on the effect of arsphenamin solutions upon the blood stream, which illuminate the mechanism of reaction to this drug under therapeutic conditions. They find, following the work of Karsner and Hanslick, that arsphenamin as a chemical substance in colloid suspension produces an agglutination of red blood cells. This property is shared by other colloids, such as acacia and gelatin, and may explain the anaphalactoid reactions which follow their use in intravenous injection. Oliver and Douglas succeeded in showing that the agglutinative power of arsphenamin solution is markedly increased by the presence of an electrolyte, such as sodium chloride, and the agglutinative power can be inhibited by colloids such as are present in blood serum. The agglutinative titer of arsphenamin seems to be fairly constant for red blood cells. The reaction is most marked in human cells and least marked in chicken cells. The arsphenamin is absorbed by the red blood cells, but no agglutination occurs except in the presence of an electrolyte. There is a drop in the tier of salt dilutions of arsphenamin if they stand in the open air. It is furthermore demonstrable that a physical change in the degree of dispersion of arsphenamin results when an electrolyte is added to the drug in solution. These authors, therefore, suggest that the action of the electrolyte, in producing an agglutination of red blood cells is primarily upon the absorbed arsphenamin of sensitized cells. In a subsequent article Oliver and Yamada demonstrated a protective effect of many hydrophilic colloids.

Cause of Early Arsphenamin Reactions.—In a subsequent article (*Jour. Pharm. and Exper. Therap.*, 1922, **19**, 393) OLIVER and YAMADA take up experimental studies into the relation of this peculiarity of

arsphenamin solutions to the clinical reactions produced by the drug. They differentiate arsphenamin reactions into early and late types, a distinction which has long been clinically recognized, and point out that the early reactions partake distinctly of the so-called anaphylactoid characteristics; while the late reactions exhibit the ill-effects incident upon the chemical base of the drug (arsenic). In a study of a series of rabbits following acute arsphenamin death, they succeeded in showing that even after use of the disodium arsphenamin salt, now so widely advocated for intravenous administration, agglutination of red blood cells occurs. They succeeded in showing that the characteristic pathologic picture of acute arsphenamin death is that of wholesale agglutination of red blood cells with the formation of multiple emboli in the terminal capillaries. Where the agglutination is minimal death does not occur immediately and the development of secondary reaction phenomena following embolism can be observed. The paper contains a series of very beautiful photographic demonstrations of the accuracy of the authors' work. Controlled studies of the effect of intravenous injection of red blood cells previously agglutinated *in vitro* by arsphenamin yielded the same clinical pictures and similar pathologic findings. The authors point out that acute arsphenamin death is identical with the clinical picture of multiple embolism as produced by the intravenous injection of oils and liquid fat, the emboli in the case of arsphenamin being composed of agglutinated red blood cells. This agglutination of red blood cells is in accord with that observed in the studies above mentioned and arises from the physical characteristics of the arsphenamin solution rather than its chemical composition. This work unites in a comprehensive study of arsphenamin reaction the observations of a number of observers. The increased pulmonary pressure noted as a feature of arsphenamin administration by Jackson and Smith, and Bissell's observations on the pulmonary pressure in fat embolism are shown to be comparable, and due to the formation of multiple emboli in the pulmonary capillaries. It has been shown that the physical properties of the arsphenamin solution are markedly influenced by the presence and efficiency of protective colloids, the character and concentration of electrolytes present and the hydrogen-ion concentration. The authors are extending their study to the late reactions to arsphenamin in the hope of ascertaining whether the physical properties of the drug have any bearing upon these reactions and of confirming the observation of observers such as Kolmer and Lucke. The authors are convinced from their observations that there is a purely chemical as distinguished from a physical factor in the late reactions to arsphenamin.

[Editor's Note.—In studies of the histologic changes produced experimentally in rabbits by arsphenamin and neoarsphenamin, Kolmer and Lucke (*Arch. Dermatol. and Syph.*, 1921, **3**, 483) found agglutination thrombi similar to those here described, but marked focal necroses as well.]

Arsenic Distribution following Arsphenamin Treatment of Children.—Clausen and Jeans (*Am. Jour. Syph.*, 1922, **6**, 567) report the result of a series of determinations of the distribution and excretion of arsenic following arsphenamin administration in children, using the analytical

method of Gutzeit (modified). "Arsphenamin rapidly disappears from the blood, but 10 per cent remaining in one hour. In the blood it is present exclusively in the plasma. The organs taking up the largest amounts are the liver and the small and large intestine. The excretion begins immediately, is very rapid at first, gradually diminishing until at the end of two weeks only traces are found. However, at the end of two or even three weeks 50 per cent is still stored in the tissues. It is excreted five times as rapidly in the stools as in the urine. The curve of excretion *via* the urine is a peculiar one and is evidently a composite of two curves. It seems likely that the curve of excretion *via* the stools would be of the same type, if the stools could be collected accurately at stated intervals. The amount of arsenic found in the cerebrospinal fluid is greater in the first hour (in some cases two hours) after the intravenous administration. The amount of arsenic found in the cerebrospinal fluid seems to depend upon the amount of inflammation present. In some children with no evidence of neurosyphilis no arsenic was found. The greatest amounts were found in those cases with evidence of the most active inflammation. Much more was found in infants with neurosyphilis than in older children similarly affected, which may explain the occasional need for intraspinal therapy (Swift-Ellis) in older children. In all patients was noted a diminishing amount of arsenic in the cerebrospinal fluid at succeeding injections and for the same time intervals. The arsenic content of the spinal fluid is at least as great in cases of cerebrospinal syphilis after intravenous administration of arsphenamin as would result from the intrathecal injection of arsphenamin serum according to the Swift-Ellis technic." It was also noted that no arsphenamin was present in the skeletal muscles, but that the drug was present in the heart muscle of the kitten.

Cause of Hutchinson's Teeth.—Nicholas, Massia and Dupasquier (*Ann. de dermat. et syphil.*, 1922, **3**, 321), in an extensive and interesting review, have endeavored to collect and correlate facts and observations tending to relate a group of clinical manifestations of osseous syphilis with one of the embryonal anlagen of the bones of the face, the "incisor bud" which as part of the frontal prominence, has an origin different from the lateral parts of the upper jaw; the latter originate according to some authorities from the first branchial arch. This conception is of particular interest as applied to the origin of Hutchinson's teeth. These the authors regard as the products of a dystrophic influence upon the embryonal anlagen, and not as either a syphilid in the strict sense or as the result of damage to the developing teeth. They suggest that the dystrophic injury is to the "incisor bud" and not to the tooth germ as such. This accounts for the appearance of Hutchinsonian lateral incisors as well as central incisors, and explains also the existence of aplasias. The authors further suggest that future studies may suggest a relationship between the dysplasias of this region in heredosyphilis and cite Hutinel's observations on their possible relation to endocrine dysfunction. The authors collected 19 cases, including 3 of their own, in which late gummatous changes were so exactly limited to the region developed from the "incisor bud" (intermaxillary bone) as to support strongly the belief that this part

of the jaw and face preserves even in the adult a certain amount of autonomy in its reaction to the Spirocheta pallida, and justifies the term "syndrome of the incisor bud." They emphasize that treatment is primarily medical treatment for syphilis, and not surgical intervention. The possibility of confusion of the gummatous process with alveolar abscess and maxillary cyst is pointed out.

OBSTETRICS

UNDER THE CHARGE OF

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The Coagulability of the Blood During Pregnancy and in the New Born.—FALLS (*Jour. Am. Med. Assn.*, 1922, **79**, 1816) divides hemorrhage complicating parturition into maternal and that of the new born. The mother loses a quantity of blood in labor which varies greatly. In 3 per cent of all cases the bleeding is serious. The amount of loss varies from 500 cc to 2 liters or more. The effect of hemorrhage in the parturient woman cannot be foretold and is not dependent upon the quantity of blood loss. We recognize that hemorrhage in both mother and child occurs from mechanical or chemical causes. The latter, the writer thinks, is confined to the new born. In this he apparently neglects the toxemia of pregnancy which produces important chemical changes in the mother's blood. He cites hemophilia as very rare in the female members of a family, but transmitted through them to the male members. Postpartum hemorrhages have been observed clinically much more frequently in patients who were delivered under ether anesthesia than in patients who had no anesthesia. A study of the blood was made to determine whether anesthesia by ether changed the coagulability of the blood. The results of these studies show that the coagulability of the blood in women before, during and after labor, when estimated by the coagulation, calcium and prothrombin tests, is within the limits of normal blood coagulability. There is the same coagulation time for the blood of mother and child. There is no evidence from these studies that pregnancy predisposes to a condition of the blood favorable for hemorrhage and certainly not to hemophilia. Postpartum hemorrhage can very rarely be ascribed to such a cause. In the normal fetus at birth the blood clots with normal rapidity and firmness. Subsequent tendencies to hemorrhage cannot be detected by coagulation tests made soon after birth. Patients who took ether had the same coagulation time as those who did not, and hence postpartum hemorrhage must depend upon something else than alteration in the coagulability of the blood occasioned by ether.

Infectious Abortion and the Human Subject.—In the *Lancet*, November 4, 1922, **2**, 979, the reports of various observers upon infec-

tious abortion in cows and the possibility of its communication to the human subject are discussed. It will be remembered that an organism known as B. abortus was isolated in 1890 by Bang, and thought to be the cause of infectious abortion in cattle. This germ can be cultivated with difficulty and compared with other well-known bacteria is remarkably inert. Another similar germ was discovered in mares. Both of these are thought to produce infectious abortion. As regards the human subject, the organism found in bovine cases is also present in many instances in milk; and such milk injected into guinea-pigs produces disease. The question whether this germ can produce pathological conditions in the human subject has been raised by Moore, because the organism has been found in the throat and tonsils of children. Larsen and Sedgwick, in examining 425 children, found this germ in 6 per cent. Antibodies were found in the blood in these cases, thus demonstrating the pathological character of the germ. It has further been shown by Evans that the bacillus of infectious abortion in cattle is closely related to the germ of Malta fever. The bacillus producing Malta fever can and not infrequently does infect the human body. The study of these cases suggest a very practical point, namely—that there are many causes of abortion in the human subject not clearly defined, and that some obscure cases may be caused by the bacilli described in this paper, conveyed through milk or drinking water.

The Use of Salvarsan During Pregnancy with a Fatal Result.—In the *Zentralblatt für Gynäkologie*, 1922, No. 41, p. 1634. KIRSTEIN describes an unusual case as follows: The patient was in her second pregnancy at eight months and had a contracted and rachitic pelvis. She came to the clinic evidently syphilitic. There was slight edema of the under portion of the thighs and abdomen; the urine contained no albumin. She was sent to a clinic for the treatment of venereal disease. In twenty days she was given 3 cc of a preparation known as cyarsal-Riedel, 2 cc kontraluisin and 1.35 cc neosalvarsan. About six weeks later there was an eruption over both breasts and the urine contained a trace of albumin. The eruption speedily disappeared and the patient was twice given injections of kontraluisin and 0.45 cc of neosalvarsan; in all 1.8 cc of neosalvarsan. Four days after the giving of the last dose the urine was evidently albuminous, and an exanthem developed over the entire body, beginning with irritation in the region of the breasts and occasioning a great deal of itching and annoyance. The patient became very cold, had violent cough and nasal catarrh. A few days later the whole body was covered with small reddish blotches, followed by moderate fever. Labor pains developed and the patient was brought to the obstetric clinic. In addition to the eruption of the skin there was edema of the face, but the urine was free from albumin. Labor slowly developed, the membranes ruptured and there were evidences of birth pressure in the feeble heart sounds and the escape of meconium. Dilatation of the cervix was but partially accomplished, and after a tedious labor a normally developed living child was born, in spontaneous labor. The placenta was naturally expelled about an hour afterward, and twenty minutes later the patient had a chill followed by fever of 104.5° F. An illness of fourteen days followed with fever without chills and the presence in the vaginal discharge on the

second day of hemolytic staphylococci in great abundance. Blood cultures on the second, nineth and fourteenth days were sterile. The patient died on the fourteenth day, having developed symptoms of catarrhal pneumonia, double femoral thrombosis and septic infection. Autopsy showed influenza-pneumonia and also an infection of the genital tract. In the right wall of the uterus there were two small abscesses connecting with the venous channels of the uterus. On closer study of the case, there was no evidence that the pneumonia was metastatic. There could be no question but that the results of the salvarsan treatment contributed greatly to the fatal issue. The writer has collected 9 deaths in parturient women following the use of salvarsan. In these cases, hemorrhagic encephalitis was the cause. Meirowski reports 20 deaths from salvarsan, where in 12 there was no doubt concerning the cause; in 5 a possible question, and in 3 the salvarsan had only an indirect effect. In the writer's clinic 39 syphilitic pregnant women have been treated, and neosalvarsan has been used in a total quantity amounting to 3.15 G. In only 1 case was there fever, and that patient received inunctions of mercury in addition.

GYNECOLOGY

UNDER THE CHARGE OF

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Myomectomy.—For the past several years the operation of myomectomy, as opposed to hysterectomy, seems to have been regaining some of its lost popularity and perhaps the foremost advocate of this operation has been MAYO (*Minnesota Med.*, 1922, **21**, 235). He prefaces his argument by stating that the menstrual cycle, aside from its function in reproduction, has a marked effect on the female during the period between puberty and menopause. All surgeons have seen the shrinkage of the uterus and shortening of the vagina accompanied by trophic changes which follow ovariectomy. The nervous and psychic changes of the normal menopause are aggravated in young women by operations which check the menstrual flow. The effect on the patient is essentially the same, whether menstruation is stopped by removing the ovaries and leaving the uterus, or removing the uterus and leaving the ovaries, according to Mayo's observations. It is probable, he thinks, that menstruation itself has some important endocrine function. Conservation of the reproductive function is of first importance, but conservation of the ovary for the continuance of its internal secretion and its effect on the production of menstruation is second only to the genera-

tive function. Even if reproduction is impossible, conservation of the ovary or some portion of it for the sole purpose of continuing menstruation is of the greatest importance. The technic of hysterectomy has been so thoroughly organized and perfected that there is a tendency to perform the operation so readily that many patients are deprived not only of the right to motherhood; but also of the function of menstruation, which is so important to the endocrine system. Hysterectomy is seldom necessary for benign myoma in a woman under thirty-five years, and demands an excellent reason in a woman under thirty. It has been argued against myomectomy that it is a more dangerous operation than hysterectomy, but the mortality in the series of the Mayo Clinic of 909 cases with 7 deaths was a trifle under 1 per cent (0.7 per cent). In cases of abdominal myomectomy the mortality was 0.5 per cent. Vaginal myomectomy gave a death rate of 2.7 per cent on account of the infection present. The statement has been made that often myomas develop after myomectomy. Only 2.56 per cent required secondary operations. In more than half of these the second operation was performed five or more years after the myomectomy, and in 1, thirteen years afterward. More than half the secondary operations were performed for inflammatory disease and in no case was a malignant condition found. In the cases in which a second operation was performed for recurrence of the myomas, the use of radium would probably be considered now. In none of the cases reported were the recurrent tumors large, because the patients, knowing their former condition, were on the alert. Hysterectomy was usually performed at the second operation, but the patient had been carried along by the myomectomy to an age in which a radical operation is of less consequence. While considering this report from the Mayo Clinic, it will be of interest to review a series of 100 consecutive myomectomies which have been reported by Bonney (*Lancet*, 1922, **2**, 745), a well known British gynecologist. He states that neither the number nor the position of the tumors within the uterus, nor the presence of degeneration, nor the accompaniment of menorrhagia or pregnancy are a bar to the successful performance of the operation. He believes, however, that patients suffering from profound anemia due to fibroids should not be treated by myomectomy, because in them the continuance of even normal periods is undesirable, so much is their blood content depleted. Moderate menorrhagic anemia however, does not contraindicate myomectomy, provided the operation is carried out so that all the tumors are removed and the uterus left behind is not too big for the involution that occurs after myomectomy to restore it to normality. One of the risks urged against myomectomy is that of menorrhagia continuing after operation, but where this occurs it is nearly always due to the surgeon's failure to achieve these two desiderata. In all cases of fibroids with menorrhagia where myomectomy is performed, Bonney believes that the uterine cavity should be opened in order to make certain that no small fibroid on the mucous surface, or mucous polypus, or great thickening of the endometrium is missed. The chief risk of an extensive myomectomy is hemorrhage during and after the operation. It can be guarded against by temporarily securing the main vessels going to the uterus, by properly placing the sutures and by cutting away sufficient tissue to leave an organ of manageable size to suture. The incision should

be a single anterior incision in the uterus with extraction of all the tumors through that incision. An anterior incision has these great advantages: if postoperative bleeding occurs, the blood accumulates in the utero-vesical space and the intestine is least likely to adhere in consequence of it; if the operator doubts that the incision is blood-tight he can suture it to the anterior abdominal wall or the back of the bladder and render it safe, while the single incision reduces the area of possible blood leakage and intestinal adhesion to a minimum. The fibroid most easily accessible through the anterior incision should be removed first and the incision should be carried right into the substance of the tumor so that there is no difficulty in finding the plane of cleavage between the tumor and capsule. This fibroid having been enucleated, the next most accessible should be reached by a secondary incision starting in the wall of the cavity left by the first tumor. In this way tumors of the posterior wall can be reached by a track which skirts around the uterine cavity but does not open it. One of the most important parts of a myomectomy is the suturing of the enucleation cavities, which usually consists of deep mattress sutures supplemented by superficial approximation sutures. The number of tumors removed by Bonney varied from 1 tumor in 49 cases to as high as 30 tumors in 1 case and the mortality of the entire series was 2 per cent.

Pneumopyelography.—Since the introduction of the method of injecting oxygen and later carbon dioxid and even air, into the various body cavities as an aid in roentgen-ray diagnosis, its use has become comparatively common and varied; however, the injection of gas into the renal pelvis has not been popularized to the extent which it deserves according to THOMPSON (*Jour. Urology*, 1922, **7**, 285). When the ureter or pelvis has been filled with an opaque solution and a roentgenogram obtained, it causes a white shadow on the plate bringing into relief only the pelvis and calices and not the kidney tissue itself, as the shadow is so dense that it obscures the tissues causing lighter shadows directly in front or behind the opaque media. For instance, the shadow of a stone in the ureter or pelvis is obscured by the heavier shadow of the opaque solution. The injection of oxygen into the ureter or renal pelvis causes no shadow at all, but creates a space which shows up black on the roentgen-ray plate, and brings into relief not only the pelvis and calices, but also the kidney tissue, as it does not obscure the shadows caused by the tissues either in front or behind. For example, the shadow of a stone will not be obscured by the oxygen and the size, shape and position of the stone can be easily determined. The black of the oxygen against the lighter shadow of the kidney substance makes a better contrast for the study of the kidney substance than does the white shadow of the opaque solution against the surrounding lighter shadow of the kidney. The apparatus required for the oxygen injections includes an oxygen tank, about 3 feet of rubber tubing in the center of which is a tube connected to a manometer, 2 cc Luer syringe barrel, a hypodermic needle large enough to fit snugly in the end of a No. 6 F. ureteral catheter, and a non-opaque ureteral catheter. The patient must be prepared in such a manner as to exclude all gas from the intestine so that no confusing shadows will be on the plate. For this purpose two ounces of castor oil should be given the night before,

a soap-sud enema is given six hours before and repeated two hours before the roentgen-ray examination. The ureters are catheterized in the usual manner, a number 6 French ureteral catheter is preferable. The oxygen is then allowed to flow into the catheter until the patient complains of a fulness in the kidney region. The pressure in the manometer is noted at this point and then oxygen is allowed to flow until the pressure has reached 20 mm. above this point and then the roentgenogram is made.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Experimental Production of Periarteritis Nodosa in the Rabbit with a Consideration of the Specific Causal Excitant.—The various describers of the 54 cases of periarteritis nodosa on record have discussed, at length, whether or not the vascular lesions constitute a disease entity or represent a peculiar invasion of the vascular structures by the "virus of syphilis" or by certain known microörganisms. Because of the rarity of the disease and its infrequent recognition during life, and inasmuch as search for an etiological agent was attempted in less than one-fourth of the reported cases and, among these, attempts at transmission of disease to animals in only three, periarteritis nodosa has afforded a small field for experimental study. Recently, HARRIS and FRIEDRICHS (*Jour. Exp. Med.*, 1922, **36**, 219) reported the clinical and autopsy findings of a negro, aged thirty-two years, in whom characteristic lesions were found in the gastroepiploic, renal and coronary arteries and to a lesser degree in the hepatic and mesenteric lymph node arteries. Macroscopically, these lesions consisted of aneurysmal dilatations which were most marked in the right kidney, where rupture of capsule had occurred, resulting in a hemoperitoneum. The lesions could be divided into three groups: (1) the inflammatory reaction in the vessel walls; (2) the resultant vascular lesions arising from those of the first group, namely, aneurysms both true and false, thrombosis and vascular rupture with extravasation of blood; and (3) retrograde lesions in the structures involved through impairment of blood supply, chiefly because of the lesions of the second group. Microscopically, the adventitia and media were especially affected. In either or both of these layers, polymorphonuclear neutrophils and fibrin with or without a zone of necrosis in the media and fragmentation of the elastic membrane were seen. In some instances, an acute cellular and fibrinous exudate extended through the media to the subendothelial layer and at

times a lymphoid or plasma cell and eosinophilic infiltration were noted in the outer vessel area. Cultures of several kidney lesions on various media remained sterile. By inoculating emulsions of the affected human organs or tissue emulsions and filtrates from rabbits previously injected with emulsions of human nodules, into the ear vein of full-grown rabbits, gross lesions consisting of aneurysms and hemorrhages in the liver and lungs of many of the rabbits were produced. In all the rabbits microscopic changes of some degree of intensity, resembling those occurring in periarteritis nodosa of man, existed. These changes consisted of infiltrations of the arterial adventitia, media and even the intima with neutrophils, eosinophiles, lymphocytes and plasma cells. Degeneration and necrosis of the media, dilatation of the vascular lumen and thrombosis were encountered. The veins were only exceptionally affected. The authors believe that the results of their experiments afford additional evidence for eliminating Treponema pallidum as the inciting cause of periarteritis nodosa, noting that the pathological character of the gross and microscopic lesions suggests a specific inciting agent, which is transmissible to rabbits and belongs to "the group of so-called filter passers."

Experimental Studies on the Etiology of Typhus Fever.—Having "shown *Jour. Exp. Med.*, 1921, **34**, 525) that the typhus virus, in inducing the typical experimental disease in guinea-pigs, readily invites invasion in the bodies of these animals of a number of bacteria, which complicate the typhus infection but, on the other hand, have no etiological relationship to the disease," OLITSKY (*Jour. Exp. Med.*, 1922, **35**, 115) has continued his investigations by means of a deductive method, so as to study the nature of any inciting agent which might reside in the virus. Accordingly, 4 cc of active citrated blood obtained from the guinea-pigs during the height of the experimental reaction was added to an equal quantity of various media, as normal rabbit plasma, normal horse serum (diluted), veal infusion broth, human ascitic fluid, under aërobic and anaërobic conditions at 37° C. After varying intervals of time, the lower 5 cc were injected intraperitoneally into a guinea-pig, the criteria of the experimental disease being the transmissibility from animal to animal, the presence of the characteristic vascular lesions particularly in brain, the absence of secondary invasions with ordinary bacteria and the development in recovered animals of immunity to subsequent injections of typhus virus. In those media from which oxygen was excluded by a petrolatum seal, the typhus virus tended to die rapidly, the viability period being twenty-four to forty-eight hours, whereas the virus survived as long as five days under aërobic conditions. In another communication (*Jour. Exp. Med.*, 1922, **35**, 121) additional observations, relating to that supposed intracellular nature and filtrability of the virus, as it exists in the organs of guinea-pigs during the height of the typhus reaction to inoculation, are presented. Fourteen experiments were made with infected spleen and brain, including three with the frozen infected tissue, two with the desiccated tissue, three with the crushed tissue and six with the ground tissue. The results of the different procedures were practically identical. Those guinea-pigs which were inoculated, intraperitoneally, with 2 cc of the infected tissue which was not disintegrated showed, after an incubation period of from

five to ten days, typical experimental typhus fever, as did those animals receiving, similarly, infected tissue which had been repeatedly frozen and thawed, desiccated, crushed or ground. However, guinea-pigs injected with 5 cc of filtrates through Berkefeld V and N candles of suspensions of the frozen, desiccated, crushed or ground infected tissues, failed to exhibit the typical experimental disease and all of those animals reinjected with active typhus virus failed to show any immunity. The author indicates the possibility of an extracellular condition of the typhus virus as shown by his experiments. Later (*Jour. Exp. Med.*, 1922, **35**, 469), OLITSKY described experiments "to show that these filtrates, which are free, so far as we can ascertain from a living multiplying agent, can occasionally induce in guinea-pigs not only the typical lesions of the disease, but also an immunity to later injections of the active virus." Of the twenty guinea-pigs, injected intraperitoneally with 5 to 10 cc of Berkefeld V and N candle filtrates of typhus infected and subsequently disintegrated spleen and brain, five showed a rise in temperature (above 104° F.) for one to three days, first noticed from two to five days after inoculation. On the nine guinea-pigs similarly inoculated with filtrates and reinjected after ten to sixteen days with active typhus virus, six showed no immunity, two showed a partial and one a complete immunity. In four of ten guinea-pigs inoculated with the filtrates and sacrificed seven days after injection, histopathological lesions characteristic of experimental typhus fever were found. The author believes that the general indications are that the substance which causes these occasional reactions is not a living organism.

Experimental Studies of the Nasopharyngeal Secretions from Influenza Patients. VI. Immunity Reactions. — Having identified "the active material pathogenic for rabbits and guinea-pigs found in the nasopharyngeal secretions of patients in the early hours of uncomplicated influenza" in the anaërobic organism (Bacterium pneumosintes) OLITSKY and GATES (*Jour. Exper. Med.*, 1922, **35**, 1) conducted a series of immunity experiments on rabbits which had recovered after the inoculation of various materials, including nasopharyngeal washings from influenza patients, suspensions of lungs of affected rabbits, and washed mass cultures of Bacterium pneumosintes. In order to arrive at the presence of protection or cross-protection, similar material was injected at varying periods after recovery. It was found that the experiments gave additional evidence of the "pathogenic character and the virtual identity of the various strains of the active agent derived from the nasopharyngeal secretions of influenzal patients with which the transmission experiments in rabbits" had been carried out. As the active material had been demonstrated to be of antigenic nature, the rabbits were protected from the effects of a second inoculation. The authors state that their experiments indicate the antigenic identity of the various strains of the active agent with each other and with Bacterium pneumosintes, and that the protection may persist for fourteen months, which was the longest period yet tested.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Physiological Effects of Exposure to Low Concentrations of Carbon Monoxide.—SAYERS and MERIWETHER (*Public Health Reports*, 1922, **37**, 1127) summarize their work as follows: (1) The exposure for six hours to 2 parts of CO in 10,000 of air caused: (*a*) Saturation of 16 to 20 per cent of the hemoglobin of the blood with CO; (*b*) very mild subjective symptoms of CO poisoning at the end of the test; (*c*) no noticeable effects after the test. (2) The exposure to 3 parts of CO caused: (*a*) Saturation of 22 to 24 per cent of the hemoglobin with CO after four hours, and 26 to 27 per cent after five hours; (*b*) symptoms at the end of two hours absent; after four hours, mild effects attributed to CO poisoning; and after five hours, moderate effects; (*c*) after-effects of four hours' exposure mild; of five hours' exposure moderate. (3) The exposure to 4 parts of CO in 10,000 caused: (*a*) Saturation of 15 to 19 per cent of the hemoglobin with CO at the end of one hour and 21 to 28 per cent at the end of two hours; (*b*) after-effects, moderate to marked. *With the subject exercising strenuously:* (1) The exposure for one hour to $2\frac{1}{2}$ parts of CO in 10,000 caused: (*a*) Saturation of 14 to 16 per cent of the hemoglobin with CO; (*b*) moderate symptoms of CO poisoning at the end of the test; (*c*) after-effects mild to moderate. (2) The exposure for one hour to 3.3 parts of CO in 10,000 caused: (*a*) Saturation of 17 per cent of the hemoglobin with CO; (*b*) mild to moderate symptoms of CO poisoning; (*c*) after-effects mild to moderate (3) The exposure for one hour to 4 parts of CO in 10,000 caused: (*a*) Saturation of 23 per cent of the hemoglobin with CO; (*b*) moderate symptoms of CO poisoning; (*c*) moderate after-effects. *With the subject at rest. Temperature and humidity high.* (1) The exposure for one hour to 3.1 parts of CO in 10,000 caused—(*a*) Saturation of 16 per cent of the hemoglobin with CO; (*c*) mild symptoms of CO poisoning; (*c*) mild moderate after-effects. *Conclusion.* (1) The combination of CO with hemoglobin takes place slowly when the subject is exposed to low concentrations and remains at rest, many hours being required before equilibrium is reached. (2) The rate of combination of CO with hemoglobin takes place much more rapidly during the first hour of exposure than during any succeeding hour, with the subject remaining at rest. (3) Strenuous exercise causes much more rapid combination of CO with hemoglobin than when the subject remains at rest. The symptoms of CO poisoning are emphasized by exercise. (4) High

temperature and humidity, with a given concentration of CO cause more rapid combination of CO with hemoglobin than do normal conditions of temperature and humidity. All symptoms and effects described in this paper are called acute in character. None of the subjects has shown any permanent deleterious effects from the exposure to CO.

The Decline in the Death Rate, 1901-1910 and 1910-1920.—Data from the Statistical Office, U. S. Public Health Service (*Public Health Reports*, 1922, **37**, 1625), show that the gross death-rate from all causes in the original registration state declined from 17.2 per 1000 in 1900 to 15.6 in 1910 and 13.9 in 1920, a decrease of 9.3 per cent in the first decade and 10.9 per cent in the second decade. Taking into consideration the fact that a secondary but severe epidemic of influenza-pneumonia occurred in the early part of 1920, the indicated decline from 1910 to 1920 is less than it would have been had 1920 been a normal year. In forty-two cities in the United States, having a population of over 100,000, the excess death-rate during the 1920 epidemic period from influenza-pneumonia alone was about 1.13 per 1000. If the same excess may be presumed to have occurred in these original registration states, the death-rate in 1920 would have been approximately 12.8 per 1000, and the decline from 1910 would have been about 18 per cent. A comparison of the specific death-rates and the expectation of life at various ages for the three periods suggests that, in addition to the accelerated decline in the mortality-rate during the decade 1910–1920, some extremely interesting and highly significant changes have taken place. Such a comparison has been made possible in a table recently published by the statistical bureau of the Metropolitan Life Insurance Company in its *Statistical Bulletin* for May, 1922. The changes in the death-rates have altered materially the complete expectation of life in 1920 as compared with 1910 and 1901. From the figures prepared by the Bureau of the Census and the Metropolitan Life Insurance Company, have been computed the decreases or increases in the expectation of life in 1910 over 1901 and 1920 over 1910. The "expectation of life" tells the story in a better way than do the mortality-rates. In 1910, at the ages of forty to eighty, the expectation of life had actually decreased over what it was in 1901. But in 1920, in spite of abnormally high mortality, especially in certain age groups, from the influenza epidemic, there was a gain in the expectation of life over 1910 in practically every age shown.

Development of Paratyphoid-enteritidis Group in Various Foodstuffs.—Koser (*Jour. Infect. Dis.*, 1922, **31**, 79) investigated several type strains of the paratyphoid-enteritidis group to gain some idea of their ability to develop in miscellaneous foodstuffs, such as various vegetables, fruits, meats and evaporated milk. The effects of different conditions, such as temperature of incubation and the hydrogen-ion concentration and the texture of the food were considered in relation to multiplication and the ability to spread throughout the foodstuff. Koser found that all the strains of the Gärtner-group multiplied readily in the liquor of several common cooked vegetables, with the exception of the highly acid sauerkraut. In the fruit juices a rapid

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destruction of the organisms occurred. In several meat products Gärtner-group organisms exhibited a marked ability to spread from one original point of inoculation throughout the foodstuff, although this occurred only under optimum temperature conditions. The author states that the development of the Gärtner-group in foodstuffs is usually not accompanied by visible alteration or spoilage, which observations are in accord with the reports of previous outbreaks of "food poisoning" caused by this group of organisms.

Clostridium Botulinum.—TANNER and DACK (*Jour. Infect. Dis.*, 1922, **31**, 92) found that the different strains of Clostridium botulinum studied in their investigation showed different resistance to dry heat. This, they state, was probably due to inherent characteristics and, in a large measure, to the age of the cultures used. At 110° C. the time of survival averaged beyond one hundred and twenty minutes. At 140° C. the variation was between sixty minutes and fifteen minutes, a rather wide variation. At higher temperatures of 160° C. and 180° C. the times of survival were short, between five and fifteen minutes. The modern methods of dry-heat sterilization seem, then, to be adequate for sterilizing apparatus which has been used for cultivating Clostridium botulinum. Young spores of Clostridium botulinum are more resistant to dry heat than old ones. Clostridium botulinum, like other pathogenic anaërobes, is commonly present in nature. In this investigation 11 of 73 of the samples of soil contained it. Three specimens of hog feces contained it, but it was not isolated from 3 specimens of cow feces. It was isolated from 1 sample of sewage. Clostridium botulinum is probably a common saprophyte widespread in nature. The results of this investigation do not conflict with those of Meyer and Geiger, who propose a regional distribution of the organism. It may be that it is more common in recently manured soils. Further investigation must be carried out before a better understanding of the characteristics of Clostridium botulinum is attained. The occurrence of the organism in stools of healthy individuals is one phase of the subject which is being investigated. In a later study TANNER and DACK (*Jour. Am. Med. Assn.*, 1922, **79**, 132–133) state that 2 of 10 specimens of feces from healthy persons were found to contain Clostridium botulinum. Five other specimens gave strong evidence of its presence. The two strains absolutely identified as Type B strains formed powerful toxins in sheep-brain medium.

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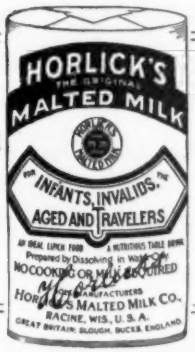

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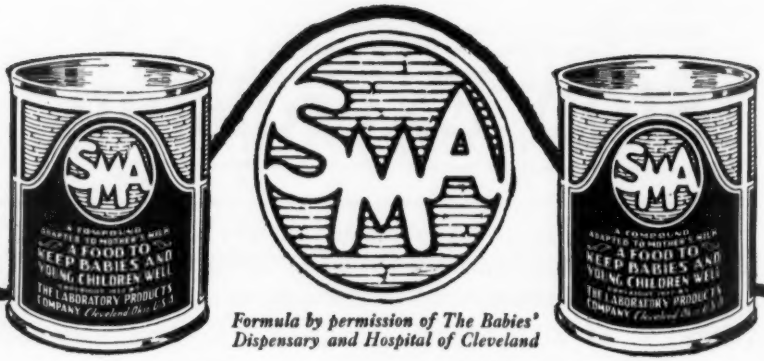
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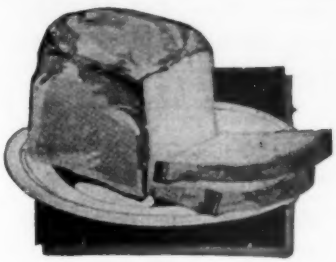

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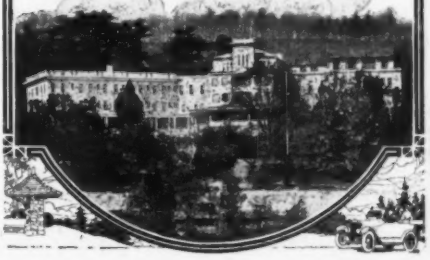

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